

**Emulation of the MONARCH-3 trial (NCT02246621) using specialty
oncology electronic health records databases**

NCT07225790

10th November 2025

1. Title Page

Title	Emulation of the MONARCH-3 (NCT02246621) trial using specialty oncology electronic health records databases
Research question & Objectives	Emulation of the MONARCH-3 (NCT02246621) trial, which compared abemaciclib–letrozole/anastrozole to letrozole/anastrozole alone with progression-free survival (PFS) as the primary endpoint and overall survival (OS) as a secondary endpoint in postmenopausal women with hormone receptor (HR)-positive [estrogen receptor (ER) and/or progesterone receptor (PR)], human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer.
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Last update date	November 10, 2025
Contributors	Primary investigators: Denys Shay, Shirley V. Wang
Study registration	Site: clinicaltrials.gov Identifier: NCT07225790
Sponsor	Organization: Food and Drug Administration Contact: n/a
Conflict of interest	SVW has been an ad hoc consultant to Exponent Inc, Cytel Inc, and MITRE a federally funded research and development center for the Centers for Medicare and Medicaid
Protocol repository	Clinicaltrials.gov
Analytic code repository	https://gitlab-scm.partners.org/drugepi/encore/monarch3-nct-02246621
Quarto study report (including annotated code and output)	https://gitlab-scm.partners.org/drugepi/encore/monarch3-nct-02246621/-/tree/main/public?ref_type=heads
encore.io¹ version	0.2.0 (see attached documentation encore.io_0.2.0.pdf)
encore.analytics¹ version	0.2.0 (https://janickweberpals.github.io/encore.analytics/)

¹ Internally-developed R package to streamline analytics across all available databases and to enhance consistency, transparency and reproducibility in variable definitions and analytic workflows across trial emulations.

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2. Abstract

This trial emulation study aims to emulate the MONARCH-3 trial (NCT02246621) using real-world specialty oncology electronic health records data and to investigate the concordance between the trial's original and the emulated treatment effect estimate on overall survival (OS). MONARCH 3 is a double-blind, randomized phase III study of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor in 493 postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who had no prior systemic therapy in the advanced setting. Patients received abemaciclib or placebo (150 mg twice daily continuous schedule) plus either 1 mg anastrozole or 2.5 mg letrozole/anastrozole, daily.

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
November 3, 2025	V1.0	NA	Initial version	NA
November 10, 2025	V1.1	- 10.2 and 10.3	- Slightly different matched cohorts and power	- Fixed minor error in the code

4. Rationale and background

Randomized controlled trials (RCTs) are generally regarded as the gold-standard of evidence for establishing efficacy of medical products. However, real-world data (RWD) are increasingly used to complement evidence from RCTs. Yet, to have confidence in the accuracy of non-interventional studies medical products and their outcomes in oncology, investigators need to know what questions can be validly answered, with which non-interventional study designs, and which analysis methods are appropriate, given the data that is available. Building on a process from the RCT DUPLICATE initiative¹⁻⁴ **EmulatioN of Comparative Oncology trials with Real-world Evidence (ENCORE)** is part of the expansion project specific to oncology and aims to emulate 12 randomized oncology RCTs using multiple EHR data sources.

The purpose of this protocol is to describe the emulation of the **MONARCH-3 trial**. MONARCH 3 is a double-blind, randomized phase III study of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor in 493 postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who had no prior systemic therapy in the advanced setting. Patients received abemaciclib or placebo (150 mg twice daily continuous schedule) plus either 1 mg anastrozole or 2.5 mg letrozole/anastrozole, daily.

The primary trial endpoint was **progression-free survival (PFS)**, with a hazard ratio (HR) for progression or death of 0.54 (95% CI, 0.41 to 0.72; $P = .000021$). The median follow-up was not reached in the abemaciclib-plus-letrozole/anastrozole group compared with **14.7 months** in the letrozole/anastrozole-alone group. The FDA granted abemaciclib approval in [March 2017](#), in combination with letrozole/anastrozole for the treatment of ER-positive, HER2-negative advanced breast cancer as initial endocrine based therapy in postmenopausal women.

Overall survival (OS) was a **secondary endpoint**. At the final OS analysis, a non-significant overall survival benefit was observed, with a median overall survival of 66.8 months in the abemaciclib group and 53.7 months in the placebo group (**HR for death**, 0.804; 95% confidence interval 0.637-1.015; $P = 0.0664$).

The PFS endpoint was published in the *JCO* on October 2, 2017 ([PMID: 28968163](#)).⁵

Updated results were published in *npj breast cancer* on January 17, 2019 ([PMID: 30675515](#)).⁶

The final OS endpoint was published in the *Ann Oncol.* on May 8, 2024 ([PMID: 38729566](#)).⁷

5. Research question and objectives

The primary and secondary research question is summarized in Table 1.

A. Primary research question and objective

Table 1. Primary and secondary research questions and objective.

Objective:	To compare the overall survival [OS] in patients who initiated abemaciclib plus letrozole/anastrozole versus patients who initiated letrozole/anastrozole alone.
Hypothesis:	Initiation of abemaciclib plus letrozole/anastrozole improves OS time as compared to initiation of letrozole/anastrozole alone.
Population (mention key inclusion-exclusion criteria):	<ul style="list-style-type: none">• Age ≥ 18 years• Postmenopausal women with ER/PR-positive, HER2-negative locally advanced or metastatic breast cancer who receive treatment without curative intent<ul style="list-style-type: none">○ The line of therapy for patients in EDB1 and EDB3 is implicitly advanced/metastatic because the line of therapy classification starts after their advanced/metastatic diagnosis in the respective database○ In EDB4, patients must explicitly have any evidence of a metastasis prior initiating abemaciclib plus letrozole/anastrozole or letrozole/anastrozole alone• No prior systemic treatment for advanced/metastatic disease• ECOG 0 or 1

Exposure:	Initiation of abemaciclib plus letrozole/anastrozole
Comparator:	Initiation of letrozole/anastrozole
Outcome:	Primary: Time to all-cause mortality (OS) Secondary: Time to next treatment (TTNT)
Time (when follow up begins and ends):	One day after the end of the assessment window until outcome, death, last observed clinical activity/last sign of the patient being alive, or data cut-off, whichever occurred earliest
Setting:	1L HR/PR-positive, HER2-negative locally advanced or metastatic breast cancer
Main measure of effect:	Hazard ratio (95% CI)

The emulation of the main protocol elements of the MONARCH-3 is illustrated side by side in **Table 2**.

Table 2. Trial emulation table summarizing the main protocol elements of the MONARCH-3 trial and the planned emulation.

Protocol component	MONARCH-3 RCT	Emulation	Comments
Eligibility criteria	<ul style="list-style-type: none"> Postmenopausal women aged ≥ 18 years with diagnosis of breast cancer Locoregionally recurrent or metastatic disease not amenable to curative resection/radiotherapy ER/PR-positive status HER2-negative status 	<ul style="list-style-type: none"> Female aged ≥ 18 years at treatment initiation with a diagnosis of breast cancer Evidence of metastatic or recurrent disease Documentation of ER/PR-positive (or -missing) status Documentation of HER2-negative (or -missing) status 	<ul style="list-style-type: none"> Although postmenopausal status is not directly captured in RWD, it is likely to be fulfilled given the alignment with the indication for the exposures of interest If ER/PR is missing and a patient received the exposures of interest, then ER/PR is likely to be positive given the alignment with the indication for the exposures of interest If HER2 is missing and a patient received the exposures of interest, then HER2 is likely to be negative given the alignment with the indication for the exposures of interest
No prior systemic therapy for advanced/metastatic disease		<ul style="list-style-type: none"> No systemic anti-cancer therapy^a following initial record indicating metastatic disease and prior to index date 	

	<ul style="list-style-type: none"> • Measurable disease per RECIST v1.1 or bone-only disease confirmed by imaging • WHO/ECOG performance status 0 or 1 • Inflammatory breast cancer • Current or prior chemotherapy or endocrine therapy (except letrozole/anastrozole) for locoregionally recurrent or metastatic breast cancer • Prior (neo)adjuvant endocrine therapy (e.g., anti-estrogens or aromatase inhibitors) with a disease-free interval \leq12 months from completion of treatment • No other malignancy within 3 years • N/A • N/A 	<ul style="list-style-type: none"> • N/A • WHO/ECOG performance status of 0 or 1 within 90 days of index date • Record of inflammatory breast cancer • NA • Treatment with (neo)adjuvant endocrine therapy \leq12 months from MBC • No prior record of non-breast cancer malignancy within 3 years • Restriction to the time period 2017-2023 • Record of systemic anti-cancer therapy other than the trial treatments^c during the exposure assessment window based on proprietary business rules 	<ul style="list-style-type: none"> • It is reasonable to assume that all patients in RWD had measurable disease if they received treatment • Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole/anastrozole • Prior non-breast cancer malignancy within 3 years is approximated with advanced prior treatments based on recommendation by the data vendor for EDB4^b • 2017 was the approval year for abemaciclib, and 2023 is the end of the available data stream
Treatment strategies	Abemaciclib+ letrozole/anastrozole vs. placebo + letrozole/anastrozole	Patients initiating abemaciclib+ letrozole/anastrozole vs. letrozole/anastrozole alone, using an exposure assessment window to capture combination treatments, based on each data vendor's proprietary business rules	Use treatment start dates to define exposure
Assignment procedures	Randomized 1:1 to abemaciclib+ letrozole/anastrozole or placebo + letrozole/anastrozole	Propensity score-based matching or weighting to emulate randomization	Balance baseline covariates to reduce confounding
Follow-up period	Time from randomization to death or censoring	After exposure assessment window until death or censoring	The purpose of an exposure assessment window is a rule-based identification of combination therapies

Outcome	Primary: Progression-free survival (PFS) per investigator assessment Secondary: Overall survival (OS)	Primary: OS Secondary: Time-To-Next-Treatment (TTNT)	Lack of good measurement of progression, so inferred by initiation of next treatment as a secondary endpoint rather than primary
Causal contrast	Intent-to-treat effect	Effect of initiating abemaciclib+ letrozole/anastrozole versus letrozole/anastrozole	Analogous to ITT; emulates initiation rather than adherence

aIncludes the following (same as antineoplastic drugs in 6.6.4) : abemaciclib, alpelisib, anastrozole, atezolizumab, bevacizumab, capecitabine, capivasertib, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, elacestrant, entrectinib, epirubicin, eribulin, etoposide, everolimus, exemestane, fluorouracil, fulvestrant, gemcitabine, goserelin, inavolisib, ixabepilone, larotrectinib, letrozole, methotrexate, nab-paclitaxel, olaparib, paclitaxel, palbociclib, pembrolizumab, pertuzumab, ribociclib, sacituzumab, talazoparib, tamoxifen, toremifene, trastuzumab, and vinorelbine.

bIncludes the following: adagrasib, afatinib, alectinib, amivantamab, atezolizumab, bevacizumab, belantamab mafodotin, bendamustine, binimetinib, bortezomib, brigatinib, cabozantinib, capmatinib, carfilzomib, cemiplimab, ceritinib, cetuximab, ciltacabtagene autoleucel, cisplatin, crizotinib, dabrafenib, dacomitinib, daratumumab, datopotomab, dexamethasone, dostarlimab, durvalumab, elotuzumab, elranatamab, encorafenib, ensartinib, entrectinib, erdafitinib, erlotinib, etoposide, fam-trastuzumab deruxtecan, fluorouracil, fruquintinib, gefitinib, gemcitabine, idecabtagene vicleucel, ipilimumab, irinotecan, isatuximab, ixazomib, lapatinib, larotrectinib, lazertinib, lenalidomide, leucovorin, levoleucovorin, linvoseltamab, lorlatinib, melphalan, mobocertinib, nivolumab, osimertinib, oxaliplatin, panitumumab, panobinostat, pembrolizumab, pemetrexed, pomalidomide, pralsetinib, ramucirumab, regorafenib, repotrectinib, retifanlimab, selinexor, selpercatinib, sotorasib, sunvozertinib, taletrectinib, talquetamab, teclistamab, telisotuzumab vedotin, tepotinib, thalidomide, tislelizumab, toripalimab, trametinib, tremelimumab, vandetanib, venetoclax, vemurafenib, vinorelbine, zenocutuzumab, ziv-afiblercept, zongertinib.

cIncludes the following: same as in a, except for abemaciclib, letrozole, and anastrozole.

6. Research methods

6.1. Data sources

6.1.1. Context and rationale for data sources

The overall ENCORE project uses data from a total of four different oncology-specific electronic health records (EHR)-derived data sources: ConcertAI, COTA, Flatiron Health, McKesson/Ontada. For ENCORE, not all databases are available for each cancer indication and the names of the databases will henceforth be blinded and referred to as ENCORE DataBase (EDB) 1, 2, 3 and 4 (the numbering does not coincide with the above order of mention of the databases).

For this trial emulation, breast cancer-specific data are available for EDB1, EDB3 and EDB4. The fitness-for-purpose of the data for the given trial emulation were assessed and considered for the final selection of the databases.

Reason for selection: All considered databases draw from a comprehensive national sample of patients with cancer in the US with detailed EHR-derived information on the information necessary to study medication effectiveness in oncology.

Strengths of data source(s): Size and detailed clinical information on oncology-specific variables and outcomes (validated composite all-cause mortality sourced from different data sources^{8,9}).

Limitations of data source(s): General limitations across all data sources include missing data, potential lack of data continuity, heterogeneous data provenance, quality/heterogeneous ascertainment of mortality endpoint data and the variability in how line of treatment is captured and curated (a more comprehensive discussion of the data sources and approaches is provided in section 7. After a comprehensive assessment of all data sources regarding their fitness for the purpose of emulating the MONARCH-3 trial.

EDB3 was found insufficient to be included in the main analysis for the following reasons.

- **Rationale for excluding of EDB3 from primary analysis:** After applying all I/E criteria, EDB3 results in a cohort with the very small sample size even before matching (Figure 6). In addition, EDB3 did not show sufficient balance in measured covariates (Figure 9).

For these reasons, only EDB1 and EDB4 will be used for the main analysis. However, EDB3 will be considered as part of a sensitivity analysis in which all databases are individually analyzed and treatment effect estimates are pooled using a meta-analytic fixed effects model (see sensitivity analysis #11 in Table 8).

Data source provenance/curation: In brief, all databases provide EHR-derived oncology-specific patient-level information which are either derived directly (e.g., through structured data fields and dropdown menu selections) from EHR and/or undergo semi-automated abstraction processes from unstructured reports. The detailed data provenance, abstraction processes and implemented business rules to curate and prioritize certain variables may vary by database and can be found in legacy publications by the data partners.

Table 3. Metadata about data sources and software.

	EDB1	EDB3	EDB4
Data Source(s):	EHR-derived	EHR-derived	EHR-derived
Study Period:	Patient identification period: 01/01/2011-04/30/2024 with follow-up information through data cut-off date on 04/30/2024	Follow-up information through June 2023 (there is no specific time period restrictions for patient eligibility)	Patient identification period: 10/01/2018-09/30/2023 with follow-up information through data cut-off date on 09/30/2023.
Eligible Cohort Entry Period:	Anytime at start of study drug initiation	Anytime at start of study drug initiation	Anytime at start of study drug initiation
Data Version (or date of last update):	Delivery: Jul 11, 2024	Delivery: Jun 16, 2023	Delivery: Oct 24, 2023 Updated (demographics): Feb 29, 2024
Data sampling/extraction criteria:	Patients are sampled if they have a confirmed diagnosis of metastatic breast cancer via abstraction on or after 1 Jan 2011, and at least 2 EHR visits on or after 1 Jan 2011. Both ICD-9 (174.x) and ICD-10 (C50.x) codes are used for the initial selection, and advanced diagnosis are then confirmed via abstraction (since ICD codes do not specify advanced diseases).	EDB3 identifies patients for curation using a structured ICD-10 diagnosis code (ICD-10 C50*), corresponding to the indication of interest, along with at least the year of diagnosis. Once this initial screening list is generated, patients are randomly selected for further review. Curation begins with confirmation of the diagnosis and diagnosis date, primarily based on pathology reports and other unstructured data sources. All patients must be over 18 years of age at the time of their first diagnosis. Certain breast cancer cases are excluded from curation. Specifically, in-situ breast cancers such as ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) without an invasive component are not eligible. However, DCIS with microinvasion or DCIS associated with Paget's disease qualifies for curation. Additionally, in-situ breast cancers that later progress to invasive carcinoma are eligible; in these cases, the diagnosis date	Breast cancer patients with an office visit in the reporting period will be included in the report with full patient history. Patients are sampled if they were diagnosed with breast cancer and with a documented visit date, within the defined reporting period, to one of the network facilities and were at least 20 years of age at the time of first diagnosis. Patients who were on a clinical trial at any point in their treatment history are excluded.

	should reflect the date of the original in-situ diagnosis, not the later invasive diagnosis.		
	Patients are ultimately selected for inclusion in data products through quality control processes that assess consistency and potential conflicts in their records. These evaluations may rely on structured data alone or a combination of structured and curated data, depending on the specific data product. Importantly, CAI does not exclude patients based on data completeness, in order to prevent the introduction of selection bias.		
Type(s) of data:	EHR-derived	EHR-derived	
Data linkage ¹ :	Mortality/date of death is a composite endpoint of structured and unstructured data from the EHR, obituary data, and the social security death index	Mortality/date of death is a composite endpoint derived from structured EHR data, manual curation, and third-party sources including obituary data and the Social Security Death Index. De-identified tokens link patients across datasets using hashed PII. Curated data is prioritized, followed by EHR and then third-party sources. Reported death dates are shifted to the nearest Sunday within four days to enhance privacy. Curated death information follows a source hierarchy: death certificate, obituary, or provider-reported date.	Mortality/date of death is a composite endpoint of structured EHR data and linked commercial data from clearinghouse providers hosted by Datavant.
Conversion to CDM ² :	No	Yes	No
Software for data management:	R 4.3.2	R 4.3.2	R 4.3.2

¹ Mortality/date of death is a composite endpoint that is often derived from various linked sources including social security death index/ Social Security Administration death master file, obituary data and EHR records

² CDM = Common Data Model

6.2. Data management

Data is stored on secure Mass General Brigham corporate provisioned and backed up servers physically located in our Mass General Brigham corporate data centers. Mass General Brigham corporate data centers are designed to insure availability of the affiliated hospitals' and research applications and IT systems in the event of a disaster. The Division follows Mass General Brigham workstation requirements which include: encryption at rest, up-to-date malware protection including antivirus, spyware detection and removal tools, CrowdStrike End Point protection installed, devices enrolled in enterprise Mobile Device Management (MDM) solution as appropriate, any laptop/computer used for business purposes must not be shared with family, friends, or other unauthorized individuals, and compliance with enterprise Password Requirements. Only authorized personnel have read-only access to raw data files.

Cleaned and analysis-ready datasets, i.e., +/- imputed one-row-per-patient tables with all required exposure, outcome and covariate variables, are stored in separate sub-directories dedicated for the specific emulated trial.

6.3. Quality control

Upon delivery, data quality procedures included checks on delivered tables and variables, per table checks, descriptives on most important measures such as demographic and stage distributions by sex at time of initial diagnosis, regimen/exposure frequency counts and time-trends and overall survival benchmarks against literature and general cancer registry statistics. The R code to reproduce the quality assessments is deposited on the Mass General Brigham-provisioned GitLab server <https://gitlab.partners.org/drugepi/encore/quality> (repository is only accessible within the Mass General Brigham network and additionally only to authorized study personnel).

6.4. Study design

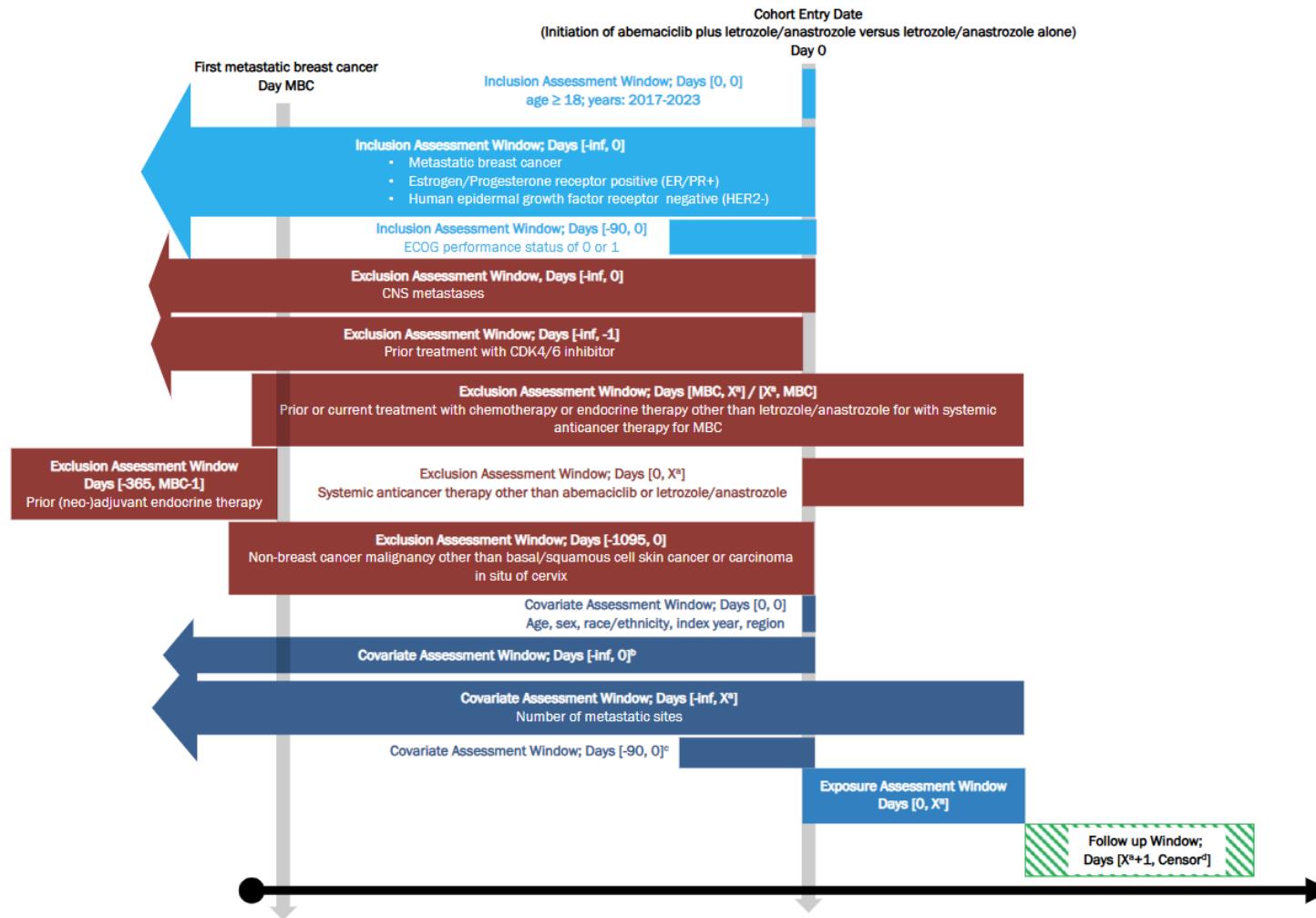
Research design (e.g. cohort, case-control, etc.): Cohort study

Rationale for study design choice: Resembles the principles of the (target) trial emulation framework.¹⁰

6.5. Study design diagram

Figure 1 depicts study design and variable measurement considerations for the emulation of the MONARCH-3 trial. The selection of key confounders/prognostic factors is driven by expert knowledge and additionally based on covariates included in the real-world prognostic score (ROPRO) which is a published and validated pan-tumor and cancer-specific prognostic score framework for overall survival.¹¹⁻¹⁵

Figure 1. Study design illustration for MONARCH-3 trial emulation.



- Proprietary business rules to define initiation of the line of therapy (including exposure assessment window) cannot be shared.
- De novo metastatic status, time initial diagnosis to T0, time from first evidence of metastatic disease to T0, smoking, family history, race/ethnicity, etc.
- Labs (albumin, hemoglobin, etc.) and vitals (BMI, etc.) that are part of the ROPRO prognostic score; see [Becker, Weerpals, et al. Ann Oncol 2020 \(doi: 10.1016/j.annonc.2020.07.013\)](https://doi.org/10.1016/j.annonc.2020.07.013)
- Intention-to-treat: death due to any reason or last observed clinical activity/sign of patient being alive or data cut-off date (whichever occurred earlier)

No observability criterion was applied because measures like continuous enrollment periods (claims data) are not available in electronic health records.

Abbreviations: MBC = metastatic breast cancer

6.6. Setting

6.6.1. Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

Time 0 in this database study is defined as the date a patient initiated abemaciclib plus letrozole/anastrozole (exposure) or letrozole/anastrozole alone (comparator) as part of their 1L systemic antineoplastic treatment for advanced/metastatic adenocarcinoma of the breast. This aims to emulate the date of randomization and cohort entry in the RCT (the time from randomization to first dose is not reported in the [clinicaltrials.gov study report](#) or the trial articles).

6.6.2. Context and rationale for study inclusion criteria

Study inclusion criteria were defined to emulate all key inclusion criteria for the trial that were deemed both clinically relevant and measurable in EHR data. See Excel appendix Table 1 (Table1_I_E) for a one-by-one evaluation. A summary of the operational definitions of the inclusion criteria that were applied for each database can be found in the Excel appendix Table 2 (Table2_I_E). In addition, the eligible time period (years) was based on the approval year of the trial's intervention drug as well as the numbers of treatment initiation. A flowchart of the study cohort assembly is provided in the appendix (10.1).

6.6.3. Context and rationale for study exclusion criteria

Study exclusion criteria were defined to emulate all key exclusion criteria for the trial that were deemed both clinically relevant and measurable in EHR data. See Excel appendix table 1 (Table1_I_E) for a one-by-one evaluation. A summary of the operational definitions of the exclusion criteria that were applied for each database can be found in the Excel appendix Table 2 (Table2_I_E). A flowchart of the study cohort assembly is provided in the appendix (10.1).

6.6.4. Context and rationale for exposure(s) of interest

The exposure and comparator were defined to emulate the agents compared for the trial, i.e., initiation of abemaciclib plus letrozole/anastrozole versus letrozole/anastrozole alone in a 1L metastatic setting.

- **EDB1:** Exposure is derived using a manually curated line of therapy (LOT) table provided by the data partner that programmatically categorizes treatment regimens into a coherent line of treatment, based on a proprietary business rule with an exposure assessment window. That is, each patient is represented with one row per curated line of therapy with corresponding information on line number, regimens as well start and end dates. Based on this table, patients are identified who received abemaciclib-plus-letrozole/anastrozole or letrozole/anastrozole-alone treatment regimen by their generic names (string match) in 1L, using the exposure assessment window; follow-up begins after the end of the exposure assessment window. The LOT implicitly only considers regimens that were given as part of a metastatic disease setting. More details and annotated code to identify initiators can be found in the 'Derive cohort EDB1' Quarto report (access within MGB network only).
- **EDB3:** Exposure is derived using a manually curated line of therapy (LOT) table provided by the data partner that programmatically categorizes treatment regimens into a coherent line of treatment, based on a proprietary business rule with an exposure assessment window. That is, each patient is represented with one row per curated line of therapy AND drug name with corresponding information on line number, regimens as well start and end dates. Based on this table, patients are identified who received only abemaciclib and letrozole/anastrozole within the first line of therapy, and

letrozole/anastrozole alone within the first line of therapy by their generic names (string match), using the exposure assessment window; follow-up begins after the end of the exposure assessment window. The LOT implicitly only considers regimens that were given as part of a metastatic disease setting. More details and annotated code to identify initiators can be found in the 'Derive cohort EDB3' Quarto report' (access within MGB network only).

- **EDB4:** For the EDB4 database, the following logic is applied.
 - Identify patients with evidence of a metastasis from the diagnosis table in which the earliest date associated with evidence of metastasis is captured as a structured field (metastasis date).
 - Identify all potential antineoplastic drugs typically used in advanced/metastatic breast cancer (see list below*). Only these are considered.
 - Identify patients who received any of the MONARCH-3 drugs within the exposure assessment window as the first antineoplastic treatment on or after the metastasis date.
 - Identify and exclude patients who received abemaciclib before the metastasis date.
 - Follow-up begins after the end of the exposure assessment window.

***Antineoplastic drugs considered:** abemaciclib, alpelisib, anastrozole, atezolizumab, bevacizumab, capecitabine, capivasertib, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, elacestrant, entrectinib, epirubicin, eribulin, etoposide, everolimus, exemestane, fluorouracil, fulvestrant, gemcitabine, goserelin, inavolisib, ixabepilone, larotrectinib, letrozole, methotrexate, nab-paclitaxel, olaparib, paclitaxel, palbociclib, pembrolizumab, pertuzumab, ribociclib, sacituzumab, talazoparib, tamoxifen, toremifene, trastuzumab, and vinorelbine.

6.6.5. Context and rationale for outcome(s) of interest

The primary outcome for the database study was defined to emulate the OS outcome for the trial, time from end of exposure assessment window to death due to any reason (OS). Operational definitions:

- **EDB1:** Time in [days, months and years] from end of exposure assessment window to death due to any reason. The date of death is de-identified to month-level granularity or (rarely) to year-level granularity and the date of death is therefore imputed to the 15th of a month or mid-year/July 2 of the year of death, respectively. If there is no indication that a patient died during the study period, the patient is censored. The censoring date is defined as the last visit or treatment encounter or data cut-off date, whichever occurred earlier. The OS endpoint is operationalized using a parameterized R function `edb1_get_os()` and more details can be found in the attached pdf documentation.
- **EDB3:** Time in [days, months and years] from end of exposure assessment window to death due to any reason. The date of death is de-identified to month-level granularity and the day of death is therefore imputed to the 15th of a month. Patients without evidence of death are censored at the earlier of the last recorded activity date or the data cut-off date. Activity dates are defined as documented in Table 4. Death dates are compiled from Electronic Medical Records (EMR), manual curation, and third-party death data, linked via de-identified tokens generated from hashed personally identifiable information (PII). Sources of death dates are prioritized as follows: (1) manual curation, (2) EMR, and (3) third-party sources. For privacy reasons, the final reported death date is shifted to the nearest Sunday within four days of the actual date. Manually curated death dates follow a prioritization hierarchy of source

documentation: death certificate first, followed by scanned obituaries or death announcements, and lastly exact dates reported by providers without other supporting documentation. The OS endpoint calculation uses a parameterized R function (`edb3_get_os()`), with detailed documentation provided in the attached PDF.

- **EDB4:** Time in [days, months and years] from end of exposure assessment window to death due to any reason. The date of death is de-identified to month-level granularity and the day of death is therefore imputed to the 15th of a month. If there is no indication that a patient died during the study period, the patient is censored. The censoring date is defined as the last date of vital signs recorded as proof that the patient was alive at that time (de-identified to week-level granularity) or data cut-off date, whichever occurred earlier. The OS endpoint is operationalized using a parameterized R function `edb4_get_os()` and more details can be found in the attached pdf documentation.

Table 4. Relevant clinical activities considered to derive last activity date for censoring.

Table / clinical activity considered	Dates considered
Adverse events	Event date
Therapy (cellular, systemic, radiation, surgery)	Start and end dates or declined intervention date, surgery date, assessed resection dates
Palliative care referral	Referral date
Visits	Contact/visit date
Vitals	Assessed date
Labs	Lab date
Biomarkers	Specimen collection date
Patient observation period	Start and end dates
Demographics	Date of most recent contact with provider, date patient was diagnosed with a second primary malignancy
Performance assessments	Documented date, reported date
Secondary diagnoses	Diagnosis date
Progression, histology, lymphovascular invasion, metastatic sites, pancoast tumor, perineural invasion	Assessed date

Stage/TNM	Assessed date
Smoking	Assessed date

6.6.6. Context and rationale for follow up

Only intention-to-treat (ITT) analyses will be conducted. Although cross-over from the exposure to the comparator can be expected, which usually biases the estimated treatment effect toward the null, this limitation also applies to the MONARCH-3 trial. In the final OS analysis reported by Goetz et al. (2024), 284 patients (86.6%) in the abemaciclib-plus-letrozole/anastrozole arm and 154 patients (93.3%) in the placebo-plus-letrozole/anastrozole arm had discontinued study treatment. After discontinuation, 38 patients (11.6%) in the abemaciclib arm and 52 patients (31.5%) in the placebo arm received a CDK4/6 inhibitor as part of subsequent therapy, which effectively constituted crossover.⁷

An as-treated analysis is not considered since in the context of oncology, reasons for discontinuation usually are due to toxicity, death or progression/non-response to the current treatment, all of which are highly correlated with the outcome under study which would hence lead to bias due to informative censoring.

6.6.7. Context and rationale for covariates.

We identified a series of covariates that are strong prognostic factors for the outcome and auxiliary covariates which may be useful to impute missing data. Such covariates comprise demographics, covariates indicating disease-severity, cancer-specific covariates as well as pathological and genetic factors. In addition, selected labs and vitals are considered since they were shown to carry a high amount of prognostic information as described in Becker, Weerpals, et al.¹¹ For these variables, additional plausibility checks and transformations are carried out. In detail, labs and vitals are individually checked if they cross a certain biologically implausible threshold (e.g., a heart rate of 0) in which cases the values are set missing and imputed in a next step. These thresholds were compiled by experienced practicing physicians and medical oncologists and are listed in appendix **Table 9** and **Table 10**.

Note that not all covariates are available across all databases used for this trial emulation. In the analytical stage, the most comprehensive model will be fit for each database individually.

Table 5. Operational definitions of key covariates used for trial emulation.

Characteristic	Harmonized analysis variable name	R function to derive covariate (see pdf in appendix)	Details ¹	Variable encoding	Assessment window
Age at index date	dem_age_index	edbx_get_demographics()	Age measured at index date	Binary (<60, 65+); modelled continuously in ROPRO ¹¹	[0;0]
Year of index date	c_year_index	De novo derived from dt_index	Calendar year in which patient initiated study treatment	Nominal (<2020, 2020+)	[0;0]
Family history	dem_family_history	edbx_get_demographics()	Family history of cancer	Logical (TRUE, FALSE)	[0;0] (no specific date is associated)

Characteristic	Harmonized analysis variable name	R function to derive covariate (see pdf in appendix)	Details ¹	Variable encoding	Assessment window
Race	dem_race	edb_get_demographics()	Race categorized as in the original RCT	Binary (Asian vs non-Asian)	[0;0]
Ethnicity	dem_ethnicity	edb_get_demographics()	Ethnicity	Hispanic, Non-Hispanic	[0;0]
Region	dem_region	edb_get_demographics()	US region patient receives care in; if given on a state level, region is manually mapped (see Table 11)	Nominal (Northeast, South, West, Midwest)	[0;0]
Practice type	dem_practice	edb_get_demographics()	Setting patient is receiving care at	Nominal (academic, community, academic & community)	[-inf;0]
Socio-economic status	dem_ses	edb_get_demographics()	Socioeconomic status (SES) index based on residence area of patient	Nominal (from '1 - Lowest SES' through '5 - Highest SES)	[-inf;0]
Smoking	c_smoking_history	edb_get_demographics()	History of current or former (= TRUE) or never (= FALSE) smoking on or anytime before index date; if there are multiple records per patient, any evidence of former/current smoking is prioritized. In EDB1, "smoking history" is unavailable for breast cancer.	Binary logical (TRUE, FALSE)	[-inf;0]
ECOG	c_ecog	edb_get_ecog()	ECOG performance status measured closest to index date within assessment window. In case of ties, the lower ECOG value is selected	Nominal (0, 1, 2, 3, 4); modelled as ordinal numeric in ROPRO ¹¹ due to I/E criteria ECOG is modelled as a binary (0, 1) covariate	[-90;0]
Stage	c_stage_initial_dx	edb_get_diagnosis_solid()	AJCC summary group stage at initial diagnosis	Ordinal numeric (from 0 to IV with sub-categories, e.g., IA1) ¹¹	[-inf;0] at initial diagnosis of primary cancer
De novo metastatic status	c_de_novo_mets_dx	edb_get_diagnosis_solid()	Evidence of presence of one or multiple metastases at/before initial diagnosis	Binary logical (TRUE, FALSE)	[-inf;0] at initial diagnosis of primary cancer

Characteristic	Harmonized analysis variable name	R function to derive covariate (see pdf in appendix)	Details ¹	Variable encoding	Assessment window
Number of metastatic sites	c_number_met_sites	edb_get_diagnosis_solid() / edb_get_number_met_sites_solid()	Number of metastatic sites for a given patient before/on index date	Integer	[-inf;X]; Proprietary business-rule-based covariate assessment window
Time between initial diagnosis to index date	c_time_dx_to_index_quartiles	edb_get_diagnosis_solid()	Time in days between initial diagnosis to index date. Quartiles will be used because there may be “negative” times intervals due to date imprecision of the lines of therapy.	Categorical (quartiles)	[-initial dx;0]
Time between earliest evidence of a metastatic and index date	c_time_met_dx_to_index_quartiles	edb_get_diagnosis_solid()	Time in days between earliest evidence of a metastatic diagnosis and index date. Quartiles will be used because there may be “negative” times intervals due to date imprecision of the lines of therapy.	Categorical (quartiles)	[met dx;0]
Albumin	c_albumin_g_l_cont	edb_get_labs()	Closest albumin measurement (in serum/plasma) relative to index date in g/L. In case of ties, the lower is selected	Continuous	[-90;0]
Alkaline phosphatase (ALP) ²	c_alp_u_l_cont	edb_get_labs()	Closest alkaline phosphatase measurement (in serum/plasma) relative to index date in U/L. In case of ties, the lower is selected	Continuous	[-90;0]
Alanine aminotransferase (ALT) ²	c_alt_u_l_cont	edb_get_labs()	Closest alanine transaminase measurement (in serum/plasma) relative to index date in U/L. In case of ties, the lower is selected	Continuous	[-90;0]
Aspartate aminotransferase (AST)	c_ast_u_l_cont	edb_get_labs()	Closest aspartate aminotransferase measurement (in serum/plasma) relative to index date in U/L. In case of ties, the lower is selected. Only used to compute AST-ALT ratio.	Continuous	[-90;0]
AST/ALT ratio	c_ast_alt_ratio_cont	edb_get_labs()	AST/ALT ratio calculated from c_ast_u_l_cont/c_alt_u_l_cont	Continuous	[-90;0]
Bilirubin ²	c_bilirubin_mg_dl_cont	edb_get_labs()	Closest bilirubin measurement (in serum/plasma) relative to index date in mg/dL. In case of ties, the lower is selected	Continuous	[-90;0]

Characteristic	Harmonized analysis variable name	R function to derive covariate (see pdf in appendix)	Details ¹	Variable encoding	Assessment window
Calcium ²	c_calcium_mg_dl_cont	edbx_get_labs()	Closest calcium measurement (in serum/plasma) relative to index date in mg/dL. In case of ties, the lower is selected	Continuous	[-90;0]
Chloride	c_chloride_mmol_l_cont	edbx_get_labs()	Closest chloride measurement (in serum/plasma) relative to index date in mmol/L. In case of ties, the lower is selected	Continuous	[-90;0]
Eosinophils/100 leukocytes ²	c_eosinophils_leukocytes_ratio_cont	edbx_get_labs()	Eosinophils/100 leukocytes in blood. In case of ties, the lower	Continuous	[-90;0]
Estrogen receptor status	c_er_status	edbx_get_biomarker()	Evidence of estrogen receptor status.	binary (positive/ negative)	[-inf; 0]
Glucose ²	c_glucose_mg_dl_cont	edbx_get_labs()	Closest glucose measurement (in serum/plasma) relative to index date in mmol/L. In case of ties, the lower is selected	Continuous	[-90;0]
Granulocyte/leukocyte ratio ²	c_granulocytes_leukocytes_ratio	edbx_get_labs()	Closest granulocyte/leukocyte ratio measurement (in blood) relative to index date. In case of ties, the lower is selected. Used to compute granulocyte/lymphocyte ratio	Continuous	[-90;0]
Hemoglobin	c_hemoglobin_g_dl_cont	edbx_get_labs()	Closest hemoglobin measurement (in blood) relative to index date in g/L. In case of ties, the lower is selected	Continuous	[-90;0]
Lactate dehydrogenase (LDH) ³	c_ldh_u_l_cont	edbx_get_labs()	Closest LDH measurement (in serum or plasma) relative to index date in U/L. In case of ties, the lower is selected	Continuous	[-90;0]
Lymphocytes	c_lymphocyte_10_9_l_cont	edbx_get_labs()	Closest lymphocytes measurement (in blood) relative to index date in 10 ⁹ /L. In case of ties, the lower is selected. Only used to compute neutrophil/lymphocyte ratio.	Continuous	[-90;0]
Lymphocyte/leukocyte ratio ²	c_lymphocyte_leukocyte_ratio_cont	edbx_get_labs()	Closest lymphocyte/leukocyte ratio measurement (in blood) relative to index date. In case of ties, the lower is selected. Used	Continuous	[-90;0]

Characteristic	Harmonized analysis variable name	R function to derive covariate (see pdf in appendix)	Details ¹	Variable encoding	Assessment window
			to compute neutrophil/lymphocyte ratio		
Monocytes ²	c_monocytes_10_9_l_cont	edbx_get_labs()	Closest monocytes measurement (in blood) relative to index date in 10 ⁹ /L. In case of ties, the lower is selected.	Continuous	[-90;0]
Neutrophils	c_neutrophil_10_9_l_cont	edbx_get_labs()	Closest neutrophils measurement (in blood) relative to index date in 10 ⁹ /L. In case of ties, the lower is selected. Only used to compute neutrophil/lymphocyte (NLR) ratio.	Continuous	[-90;0]
Neutrophil/lymphocyte ratio ²	c_neutrophil_lymphocyte_ratio_cont	edbx_get_labs()	Neutrophil/lymphocyte (NLR) ratio calculated from c_neutrophil_10_9_l_cont/ c_lymphocyte_10_9_l_cont	Continuous	[-90;0]
Platelets	c_platelets_10_9_l_cont	edbx_get_labs()	Closest platelets measurement (in blood) relative to index date in 10 ⁹ /L. In case of ties, the lower is selected	Continuous	[-90;0]
Progesterone receptor status	c_pr_status	edbx_get_biomarker()	Evidence of <u>any</u> PR mutation present. If patient has multiple measurements, any evidence of a mutation is prioritized. In case of ties, the closest measurement relative to index date is selected	Binary (positive/ negative)	[-inf;0]
Protein	c_protein_g_l_cont	edbx_get_labs()	Closest protein measurement (in serum/plasma) relative to index date in g/L. In case of ties, the lower is selected	Continuous	[-90;0]
Urea nitrogen ²	c_urea_nitrogen_mg_dl_cont	edbx_get_labs()	Closest urea nitrogen measurement (in serum/plasma) relative to index date in mg/L. In case of ties, the lower is selected	Continuous	[-90;0]
Systolic blood pressure ²	c_sbp_cont	edbx_get_vitals()	Closest systolic blood pressure (in mmHg) measurement. In case of ties, the lower is selected	Continuous	[-90;0]
Diastolic blood pressure	c_dbp_cont	edbx_get_vitals()	Closest diastolic blood pressure (in mmHg) measurement. In case of ties, the lower is selected.	Continuous	[-90;0]

Characteristic	Harmonized analysis variable name	R function to derive covariate (see pdf in appendix)	Details ¹	Variable encoding	Assessment window
Body mass index (BMI) ²	c_bmi_cont	edb_get_vitals()	Closest BMI measurement (in kg/m ²) relative to index date. In case of ties, the lower is selected.	Continuous	[-90;0]
Heart rate ²	c_hr_cont	edb_get_vitals()	Closest heart rate measurement (in bpm) relative to index date. In case of ties, the lower is selected	Continuous	[-90;0]
Oxygen saturation	c_oxygen_cont	edb_get_vitals()	Closest heart rate measurement (in bpm) relative to index date. In case of ties, the lower is selected	Continuous	[-90;0]

¹x stands for the pseudonymized number of the respective database, i.e., EDB1, EDB3 or EDB4

²For calculation of ROPRO prognostic score¹¹, this variable is log transformed.

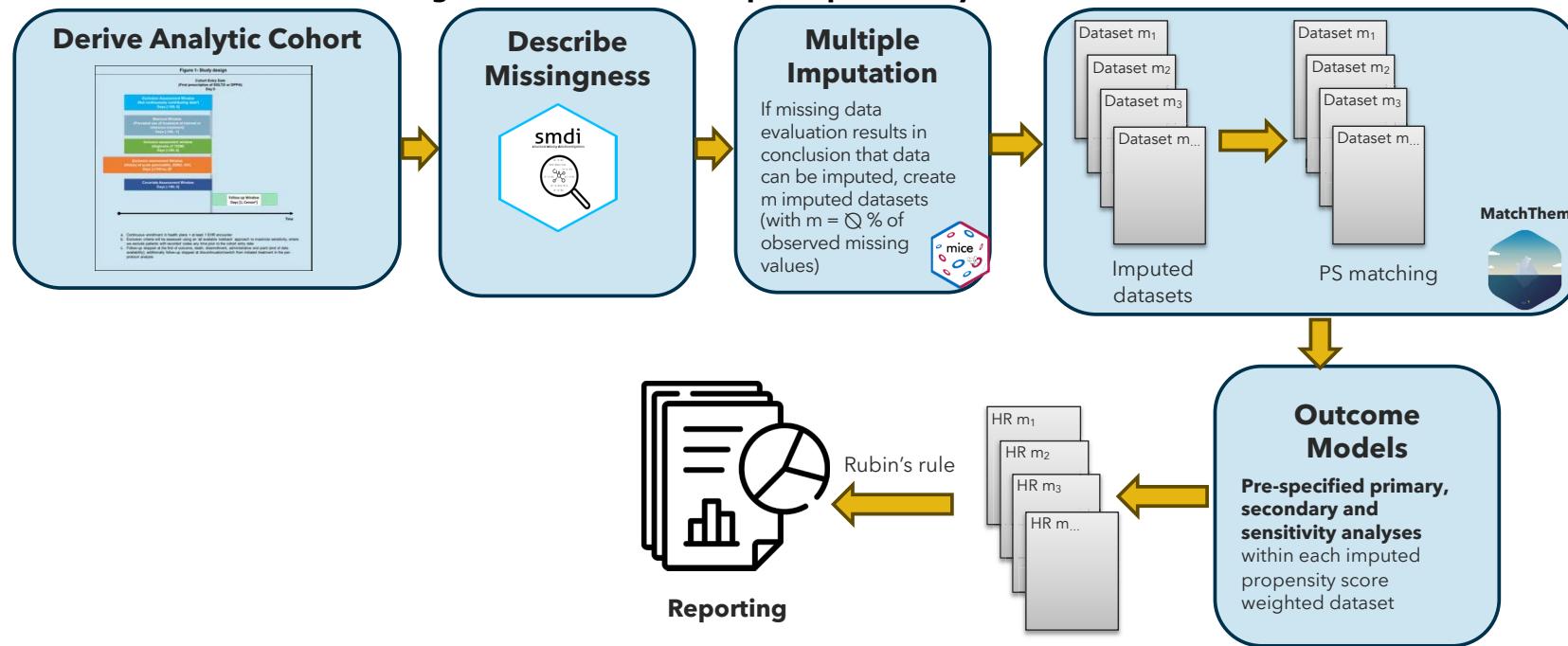
³For calculation of ROPRO prognostic score¹¹, this variable is log-log transformed.

6.7. Data analysis

6.7.1. Context and rationale for analysis plan

To emulate the MONARCH-3 trial, the following analytical workflow will be used (Figure 2). First, an analytical cohort with covariates on key eligibility criteria and prognostic factors will be derived across all databases. To ensure reproducibility and consistency throughout the entire ENCORE project, the internally developed *encore.io* R package streamlines this process using the functions referenced in Table 5. Operational definitions of key covariates used for trial emulation.(code documentation see appendix).¹⁶ The analytical cohort will be derived by first identifying a metastatic breast cancer inception cohort of initiators of abemaciclib plus letrozole/anastrozole or letrozole/anastrozole alone in the first-line setting as described in section 6.6.4. Next, key eligibility criteria will be applied in which patients with missing values are considered eligible in the respective attrition steps to allow thorough missing data investigations.

Figure 2. Illustration of principled analytical workflow.



Once a full analytic cohort is built, principled missing data investigations will be employed to empirically assess assumptions on potentially underlying missingness mechanisms according to Rubin's classification of missing data (i.e., missing completely at random [MCAR], missing at random [MAR] and missing not at random [MNAR]).¹⁷ To that end, we will adopt a principled process on missing data that was developed as part of an FDA Sentinel Innovation Center causal inference workstream that empirically evaluates different aspects across partially observed covariates based on three group diagnostics (Table 6).^{18,19} In brief, the first group diagnostics computes distributions and absolute standardized mean differences (ASMD) between patients with and without an observed value for a given partially observed covariates. If missingness can be explained by observed covariates such as in MAR mechanisms, patient characteristics will significantly differ which will (in analogy to propensity scores) be indicated by $ASMDs > 0.1$. In addition, Hoteling's²⁰ and Little's²¹ tests additionally provide formal hypothesis tests for such comparisons in which high test statistics and a rejection of the null hypothesis would provide evidence for differences in the distribution of patient characteristics and suggest the underlying mechanism is not MCAR or MNAR. Group 2 diagnostics assess the ability to predict missingness based on observed covariates by fitting a classification model to predict the missingness indicator of the partially observed covariate. To that end, we will fit a random forest (RF) classification model using observed covariates with a 70/30 train-test split of the complete cohort. A sufficiently high area under the receiver operating characteristic curve (AUC) metric of the test dataset may demonstrate that missingness can be predicted well and could point towards MAR as a likely mechanism as opposed to an $AUC \sim 0.5$ which would suggest MCAR or MNAR. Group 3 diagnostics evaluates the association between the missingness indicator of the partially observed covariates and the outcome (OS). If the missingness of a confounder cannot be explained or approximated by observed covariates and a difference in the outcome is observed depending on the missingness indicator (e.g., $HR_{\text{missingness indicator}} \neq 1$), this may be indicative of an underlying MNAR mechanism. These empirical diagnostics will be implemented through the smdi R package²² and be further enhanced by clinical expert knowledge.

Table 6. Diagnostics to empirically differentiate and characterize missing data mechanisms.

	Group 1 Diagnostics		Group 2 Diagnostics	Group 3 Diagnostics
Diagnostic metric	Absolute standardized mean difference (ASMD)	P-value Hoteling ²⁰ Little ²¹	Area under the receiver operating curve (AUC)	Log HR (missingness indicator)
Purpose	Comparison of distributions between patients with vs. without observed value of the partially observed covariate.		Assessing the ability to predict missingness based on observed covariates.	Check whether missingness of a covariate is associated with the outcome (differential missingness).
Example value	ASMD = 0.1	p-value < 0.001	AUC = 0.5	log HR = 0.1 (0.05 to 0.2)
Interpretation	<p><u><0.1^a</u>: no imbalances in observed patient characteristics; missingness may be likely completely at random or not at random (~MCAR, ~MNAR).</p> <p><u>>0.1^a</u>: imbalances in observed patient characteristics; missingness may be likely at random (~MAR).</p>	<p>High test statistics and low p-values indicate differences in baseline covariate distributions and null hypothesis would be rejected (~MAR).</p>	<p>AUC values ~ 0.5 indicate completely random or not at random prediction (~MCAR, ~MNAR).</p> <p>Values meaningfully above 0.5 indicate stronger relationships between covariates and missingness (~MAR).</p>	<p>No association in either univariate or adjusted model and no meaningful difference in the log HR after full adjustment (~MCAR).</p> <p>Association in univariate but not fully adjusted model (~MAR).</p> <p>Meaningful difference in the log HR also after full adjustment (~MNAR).</p>

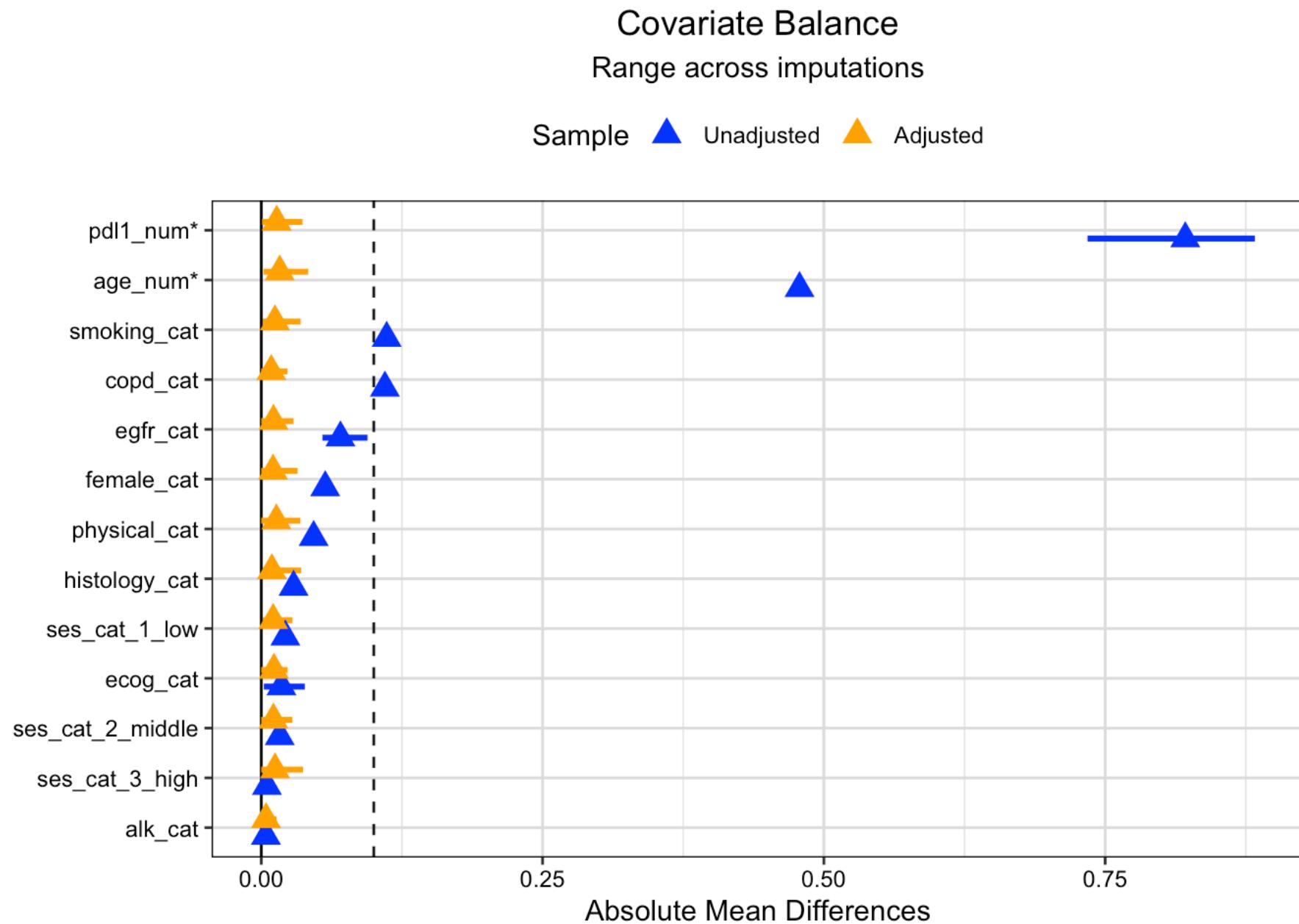
Abbreviations: ASMD = Median absolute standardized mean difference across all covariates, AUC = Area under the curve, CI = Confidence interval, MAR = Missing at random mechanism in which the missingness probability depends on observed covariates, MCAR = Missing completely at random mechanism in which each patients has the same missingness probability, MNAR(unmeasured) = Missing not at random mechanism in which the missingness can only be explained by a covariate which is not observed in the underlying dataset, MNAR(value) = Missing not at random mechanism in which the missingness just depends on the actual value of the partially observed confounder of interest itself.

^a Analogous to propensity score-based balance measures.²³

While the MAR assumption is a strong assumption to hold across all considered covariates, it was shown that especially in the context of partially observed covariate data (as opposed to missing exposure and outcome data), only mechanisms in which a covariate causes its own missingness leads to critical bias (MNAR).^{24,25} In such situations, multiple imputation can have significant advantages over a complete case analysis since additional information (auxiliary covariates and missing indicator

variables) can be included in imputation algorithms which can make the MAR assumption holding more plausible and increase efficiency in treatment effect estimates since all patients and critical covariates can be retained and variances can be realistically estimated, considering both the general sampling error and the error introduced by missing data.^{26,27} Hence, multiple imputation with flexible, non-parametric random forest imputation algorithms²⁸ (mice R package²⁹) will be used for this trial emulation. The number of imputed datasets (m) will be determined for each database separately based on the average proportion missingness observed in the analytic cohort and results from the above-referenced missing data investigations will inform the choice of appropriate sensitivity analyses.

Figure 3. Covariate balance across imputed datasets (simulated example).



To estimate the treatment effects for abemaciclib plus letrozole/anastrozole using propensity score matching across imputed datasets we will apply the “within” approach using the “MatchThem” R package.^{30,31} That is, propensity score matching and the estimation of the treatment effect are performed in each imputed dataset separately and resulting treatment effect estimates are combined using Rubin’s rule. In this study, this will be implemented by matching eligible patients on their propensity to initiate abemaciclib plus letrozole/anastrozole using a 1:1 nearest neighbor matching algorithm without replacement and a caliper of 1% of the standard deviation of the propensity score. The resulting covariates balance will be assessed by computing and visualizing ASMDs before and after matching across datasets. As compared to a single dataset matching approach, this can lead to a range of ASMDs per covariate due to random variation across imputed datasets for which an example (using simulated data) is illustrated in Figure 3. If sufficient balance can be established, a Cox proportional hazards regression model will be fit to estimate the marginal average treatment effect in the matched population. Confidence intervals will be estimated using cluster-robust standard errors.³² As a secondary endpoint, we will additionally estimate the median OS survival time difference between the two exposure groups using the Kaplan-Meier method. It should be noted that due to administrative and de-identification purposes, the date of death is often only available at the month- or year-granularity level, in which case the date of death will be imputed to the 15th of a month or July 2nd of a year, respectively (depending on the database). In rare cases, this can lead to negative/implausible follow-up times if the date of death is very close to the index date. These patients will be excluded from the analysis.

The final hazard ratio and median OS survival time difference estimates for each database will then be combined using Rubin’s rule.^{29,33} To arrive at a single estimate across databases, the final estimates will be summarized through a meta-analytic fixed effects model.³⁴ A summary of the analytic approach is summarized in Table 7 and an example workflow with simulated data and annotated code can be found [here](#).

A. Analyses

Table 7. Primary, secondary, and subgroup analysis specification

Hypothesis:	Initiation of abemaciclib plus letrozole/anastrozole decreases the hazard of all-cause mortality as compared to initiation of letrozole/anastrozole alone
Exposure contrast:	Initiation of abemaciclib plus letrozole/anastrozole vs letrozole/anastrozole alone
Primary outcome:	Time to all-cause mortality (OS)
Secondary outcome:	Time-to-next-treatment (TTNT) defined as a composite outcome of all-cause mortality or adding or switching to a second-line treatment. ^{35,36}
Databases used:	EDB1 and EDB4 (primary analysis); EDB3 (sensitivity analysis)
Time period:	From 2017 (approval year for abemaciclib) - 2023
Analytic software:	R 4.3.2. Version control of code and R packages will be established through git and Posit package manager, respectively. All packages are frozen to their most recent version as of April 25, 2024.
Model(s): (provide details or code)	See example code here . The annotated code for the trial emulation will be hosted at https://drugepi.gitlab-pages.partners.org/encore/ monarch3-nct-02246621/ (access only through MGB network for authorized personnel)
Confounding adjustment method	Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.
	1:1 propensity score nearest neighbor matching without replacement and a caliper of 1% of propensity score standard deviation
Missing data methods	Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.
	Multiple imputation by chained equations using a random forest imputation model across all covariate types. The number of imputed datasets will be determined by the average proportion of missing values across all partially observed covariates. Imputation models will include all variables of the substantiative model, i.e., exposure, outcome, confounders/prognostic factors and additional auxiliary covariates.
Subgroup Analyses	List all subgroups
	In subgroup analysis, multiple imputation, propensity score matching and balance assessment will be conducted within each subgroup separately. The treatment effect will be estimated for each stratum separately (stratum-specific effects).
	<ol style="list-style-type: none"> 1. Age (<65, ≥65) 2. Race (Asian vs. Non-Asian) 3. ECOG (0, 1) 4. Hormone receptor status (ER and PR-positive vs. Other)

Table 8. Sensitivity analyses – rationale, strengths and limitations.

What is being varied? How?		Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Sensitivity #1	Caliper matching on ROPRO prognostic score instead of propensity score	Matching patients on validated prognostic score may be more beneficial to control for (unmeasured) confounding	Matches patients on validated prognostic score that incorporates weights of key prognostic factors	Limited experience on how to optimally use prognostic scores and should be seen as an <u>experimental</u> sensitivity analysis
Sensitivity #2	ATO weighting instead of matching	Weights that resemble the average treatment effect in the overlap population (ATO) create a clinical equipoise population which is comparable to an RCT	ATO weighting usually results in excellent balance and clinical equipoise	Estimates the average treatment effect among the overlap patients which may not be comparable to target population anymore
Sensitivity #3	SMR/ATT weighting instead of matching. Here symmetric trimming (i.e., setting all weights lower/higher than that at a given quantile to the weight at the quantile) of extreme weights may be considered with the quantiles chosen based on weight distribution and resulting balancing performance.	SMR weighting retains all patients and resembles the same estimand as matching	ATT weighting retains all patients	Patients with extreme weights after trimming may bias the analysis
Sensitivity #4	Censoring date is changed to 3 months before data cut-off date	For all databases, information on mortality comes from different data sources which are updated asynchronously. To account for the potential lag of updated mortality information (<i>ghost-time bias</i> ³⁷), the censoring for patients without mortality event in the whole patient identification period will be moved to last sign of patients being alive/visit or 3 months before data cut-off date, whichever occurred earlier. ³⁸	Approach implements a more conservative censoring rule	Approach addresses ghost-time bias by censoring patients without a recorded death event earlier
Sensitivity #5	Delta imputation models for MNAR (tipping point analysis)	Primary multiple imputation analysis assumes MAR which	Estimates impact of deviations from MAR assumption on final	Delta parameters must be assumed and results are complex to interpret in

		may not hold for every covariate	treatment effect estimates for key covariates	multivariate missingness settings; just most important covariates or those with highest suspicion of being MNAR will be evaluated
Sensitivity #6	Re-weighting of strong risk factors and/or treatment effect modifiers distribution to match that of MONARCH-3	In the presence of effect modification, treatment effect estimates may be different if the distribution of strong risk factors/effect modifiers is different in the emulated cohort versus the trial cohort	Re-weighting adjusts for differences in distributions of key risk factors and/or treatment effect modifiers (see subgroup analysis in Table 7)	Re-weighting risk factors/potential effect modifiers to match the MONARCH-3 trial and simultaneously balancing them across treatment groups may be challenging due to differences in measurement
Sensitivity #7	Including patients who have had at least 1 visit 90 days prior to treatment initiation	EHRs are often lacking data continuity, and this analysis uses the requirement of 1 visit as a proxy for continuous observation periods	Considers aspect of data continuity	There may be patients who are put on treatment immediately in which case they are falsely excluded
Sensitivity #8	Using all available calendar time	This analysis explores potential confounding related to calendar time, evolving clinical practice patterns, and access to therapies.	Aims to assess the extent of confounding introduced by changes in time, treatment practices, and access to therapies.	We expect the results to be more confounded due to calendar time.
Sensitivity #9	Missingness is handled by restricting to patients with complete observations on a subset of the most important confounders (“complete cases”).	Instead of imputing data, this sensitivity analysis restricts the analysis cohort to patients with complete observations on key confounders	Data will not be imputed and missingness is assumed to be missing completely at random	The restriction to complete cases will significantly decrease sample size. To limit the attrition of patients with partially observed covariates, it won’t be possible to use all covariates used in the main analysis propensity score model, but only consider key covariates with overall low proportions of missingness (age, sex, etc.)
Sensitivity #10	Exclusion of patients with >1 year between metastasis diagnosis and index date	This sensitivity analysis varies the inclusion criteria by excluding patients whose index date (treatment start) is >1 year after their metastatic diagnosis date which is	Helps ensure that treatment reflects initial first-line treatment of metastatic disease, not late-line therapy.	Exclusion of further patients results in a smaller cohort size which may reduce statistical power.

		clinically unrealistic or implausible for a first-line treatment		
Sensitivity #11	Addition of EDB3	EDB3 is not considered in primary analyses for reasons given in section 6.1.1.	Increased sample size and potentially broader coverage of general US cancer population	See limitations listed in section 7.
Sensitivity #12	Descriptive analysis of switching/crossover patterns in the trial and its emulation	This sensitivity analysis assesses crossover patterns comparatively in the trial and its emulation	Help to understand the potential concordance/discordance of treatment effects between the trial and its emulation	Analysis is on the description level, which may limit conclusions

7. Limitation of the methods

- Missingness in prognostic factors is a major challenge which is addressed in this emulation by multiple imputation using a non-parametric imputation algorithm. Multiple imputation usually assumes that missingness can be explained by observed characteristics, which may be empirically evaluated using principled missingness diagnostics, but the true underlying missingness mechanisms are usually unknown. Nevertheless, multiple imputation makes use of additional information (auxiliary covariates) which can render the underlying missingness assumptions more plausible. In addition, assumptions for alternative missing data approaches like complete case analysis or the “missing indicator approach” come with even stronger assumptions and additionally have the limitation of significantly reduced sample sizes, especially when comprehensively adjusting for known confounders and prognostic factors.
- Data continuity is a major challenge in EHR databases since “guaranteed” observable periods (such as continuous enrolment periods in administrative claims data) do not exist which may lead to measurement error in key covariates and exposure misclassification. Sensitivity analysis #7 tries to address this requiring patients to have had at least one visit before the index date which increases the likelihood that a patient was not only diagnosed at the respective center but is also regularly seen.
- Balancing patients on calendar year is not possible since calendar year shows instrumental variable-like behaviors (see Figure 11), i.e., it perfectly predicts treatment assignment and does not have any association with the outcome other than through the exposure. This assumption is formally untestable but clinically reasonable since there has not been any other significant change in treatment paradigms for MONARCH-3-like postmenopausal, HR-positive, HER2-negative metastatic breast cancer populations other than introduction of abemaciclib plus letrozole/anastrozole. The improvements in radiation of brain metastases may be the only exception, but it is expected that this may be of negligible significance for the scope of this emulation.

8. Protection of human subjects

This study has been approved by the Brigham and Women’s Hospital Institutional Review Board.

9. References

1. Franklin JM, Pawar A, Martin D, et al. Nonrandomized Real-World Evidence to Support Regulatory Decision Making: Process for a Randomized Trial Replication Project. *Clin Pharmacol Ther.* Apr 2020;107(4):817–826. doi:10.1002/cpt.1633
2. Franklin JM, Patorno E, Desai RJ, et al. Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies: First Results From the RCT DUPLICATE Initiative. *Circulation.* Mar 9 2021;143(10):1002–1013. doi:10.1161/CIRCULATIONAHA.120.051718
3. Franklin JM, Glynn RJ, Suissa S, Schneeweiss S. Emulation Differences vs. Biases When Calibrating Real-World Evidence Findings Against Randomized Controlled Trials. *Clin Pharmacol Ther.* Apr 2020;107(4):735–737. doi:10.1002/cpt.1793
4. Wang SV, Schneeweiss S, Initiative R-D, et al. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. *JAMA.* Apr 25 2023;329(16):1376–1385. doi:10.1001/jama.2023.4221
5. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol.* Nov 10 2017;35(32):3638–3646. doi:10.1200/JCO.2017.75.6155
6. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer.* 2019;5:5. doi:10.1038/s41523-018-0097-z
7. Goetz MP, Toi M, Huober J, et al. Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2- advanced breast cancer: final overall survival results of MONARCH 3. *Ann Oncol.* Aug 2024;35(8):718–727. doi:10.1016/j.annonc.2024.04.013
8. Curtis MD, Griffith SD, Tucker M, et al. Development and Validation of a High-Quality Composite Real-World Mortality Endpoint. *Health Serv Res.* Dec 2018;53(6):4460–4476. doi:10.1111/1475-6773.12872
9. Dong S, Kansagra A, Kaur G, et al. Validation of a Composite Real-World Mortality Variable Among Patients With Hematologic Malignancies Treated in the United States. *JCO Clin Cancer Inform.* Apr 2025;9:e2400233. doi:10.1200/CCI-24-00233
10. Hernan MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. *JAMA.* Dec 27 2022;328(24):2446–2447. doi:10.1001/jama.2022.21383
11. Becker T, Weerpals J, Jegg AM, et al. An enhanced prognostic score for overall survival of patients with cancer derived from a large real-world cohort. *Ann Oncol.* Nov 2020;31(11):1561–1568. doi:10.1016/j.annonc.2020.07.013
12. Becker T, Mailman M, Tan S, Lo E, Bauer-Mehren A. Comparison of overall survival prognostic power of contemporary prognostic scores in prevailing tumor indications. *Medical Research Archives.* 2023;11(4)
13. Arkenau HT, Barriuso J, Olmos D, et al. Prospective validation of a prognostic score to improve patient selection for oncology phase I trials. *J Clin Oncol.* Jun 1 2009;27(16):2692–6. doi:10.1200/JCO.2008.19.5081
14. Loureiro H, Becker T, Bauer-Mehren A, Ahmadi N, Weerpals J. Artificial Intelligence for Prognostic Scores in Oncology: a Benchmarking Study. *Front Artif Intell.* 2021;4:625573. doi:10.3389/frai.2021.625573
15. Loureiro H, Roller A, Schneider M, Talavera-Lopez C, Becker T, Bauer-Mehren A. Matching by OS Prognostic Score to Construct External Controls in Lung Cancer Clinical Trials. *Clin Pharmacol Ther.* Feb 2024;115(2):333–341. doi:10.1002/cpt.3109
16. Weerpals J, Wang SV. The FAIRification of research in real-world evidence: A practical introduction to reproducible analytic workflows using Git and R. *Pharmacoepidemiol Drug Saf.* Jan 2024;33(1):e5740. doi:10.1002/pds.5740
17. Rubin DB. Inference and missing data. *Biometrika.* 1976;63(3):581–592.
18. Weerpals J, Raman SR, Shaw PA, et al. A Principled Approach to Characterize and Analyze Partially Observed Confounder Data from Electronic Health Records. *Clin Epidemiol.* 2024;16:329–343. doi:10.2147/CLEP.S436131
19. Sondhi A, Weerpals J, Yerram P, et al. A systematic approach towards missing lab data in electronic health records: A case study in non-small cell lung cancer and multiple myeloma. *CPT Pharmacometrics Syst Pharmacol.* Sep 2023;12(9):1201–1212. doi:10.1002/psp4.12998
20. Hotelling H. The generalization of Student's ratio. 1931;

21. Little RJ. A test of missing completely at random for multivariate data with missing values. *Journal of the American statistical Association*. 1988;83(404):1198–1202.

22. Weerpals J, Raman SR, Shaw PA, et al. smdi: an R package to perform structural missing data investigations on partially observed confounders in real-world evidence studies. *JAMIA Open*. Apr 2024;7(1):ooae008. doi:10.1093/jamiaopen/ooae008

23. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*. May 2011;46(3):399–424. doi:10.1080/00273171.2011.568786

24. Moreno-Betancur M, Lee KJ, Leacy FP, White IR, Simpson JA, Carlin JB. Canonical Causal Diagrams to Guide the Treatment of Missing Data in Epidemiologic Studies. *Am J Epidemiol*. Dec 1 2018;187(12):2705–2715. doi:10.1093/aje/kwy173

25. Moreno-Betancur M, Lee KJ, Leacy FP, Simpson JA, Carlin JB. Correction to: "Canonical causal diagrams to guide the treatment of missing data in epidemiologic studies". *Am J Epidemiol*. Mar 4 2025;194(3):877–880. doi:10.1093/aje/kwae406

26. Bartlett JW, Seaman SR, White IR, Carpenter JR, Alzheimer's Disease Neuroimaging I. Multiple imputation of covariates by fully conditional specification: Accommodating the substantive model. *Stat Methods Med Res*. Aug 2015;24(4):462–87. doi:10.1177/0962280214521348

27. Weerpals J, Shaw PA, Lin KJ, et al. High-dimensional multiple imputation (HDMI) for partially observed confounders including natural language processing-derived auxiliary covariates. *Am J Epidemiol*. Jan 22 2025;doi:10.1093/aje/kwaf017

28. Shah AD, Bartlett JW, Carpenter J, Nicholas O, Hemingway H. Comparison of random forest and parametric imputation models for imputing missing data using MICE: a CALIBER study. *Am J Epidemiol*. Mar 15 2014;179(6):764–74. doi:10.1093/aje/kwt312

29. Van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *Journal of statistical software*. 2011;45:1–67.

30. Leyrat C, Seaman SR, White IR, et al. Propensity score analysis with partially observed covariates: How should multiple imputation be used? *Stat Methods Med Res*. Jan 2019;28(1):3–19. doi:10.1177/0962280217713032

31. Pishgar F, Greifer N, Leyrat C, Stuart E. MatchThem::: matching and weighting after multiple imputation. *arXiv preprint arXiv:200911772*. 2020;

32. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med*. Mar 30 2014;33(7):1242–58. doi:10.1002/sim.5984

33. Rubin DB. Multiple imputation. *Flexible imputation of missing data, second edition*. Chapman and Hall/CRC; 2018:29–62.

34. Schwarzer G CJ, Rücker G. *Meta-Analysis with R*. vol 4784. Springer; 2015.

35. Rugo HS, Finn RS, Dieras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat*. Apr 2019;174(3):719–729. doi:10.1007/s10549-018-05125-4

36. Merola D, Young J, Schrag D, Lin KJ, Alwardt S, Schneeweiss S. Effectiveness research in oncology with electronic health record data: A retrospective cohort study emulating the PALOMA-2 trial. *Pharmacoepidemiol Drug Saf*. Apr 2023;32(4):426–434. doi:10.1002/pds.5565

37. Jacobs EJ, Newton CC, Wang Y, Campbell PT, Flanders WD, Gapstur SM. Ghost-time bias from imperfect mortality ascertainment in aging cohorts. *Ann Epidemiol*. Oct 2018;28(10):691–696 e3. doi:10.1016/j.annepidem.2018.06.002

38. Chen L, Fajardo O, Huntley M, Meyer A-M, Taylor M. Use of last clinical activity date in overall survival analysis with real world data. WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA; 2021:116–116.

39. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics*. 1983:499–503.

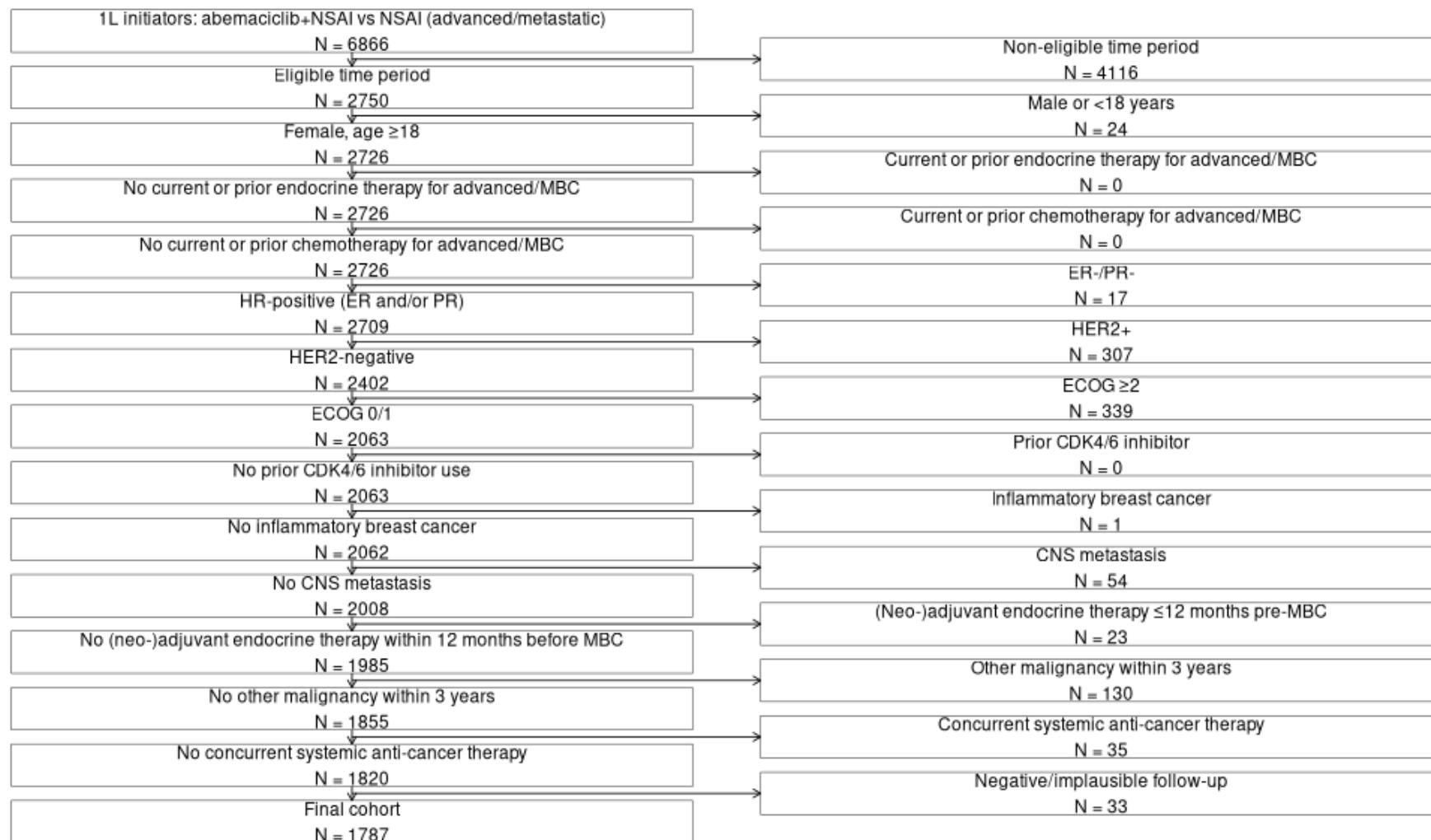
10. Appendices

10.1. CONSORT diagrams

The following CONSORT attrition diagrams depict the process to select eligible MONARCH-3-like populations in EDB1, EDB3 and EDB4 for the main analysis, respectively.

Figure 4. CONSORT attrition to select eligible MONARCH-3-like populations in EDB1.

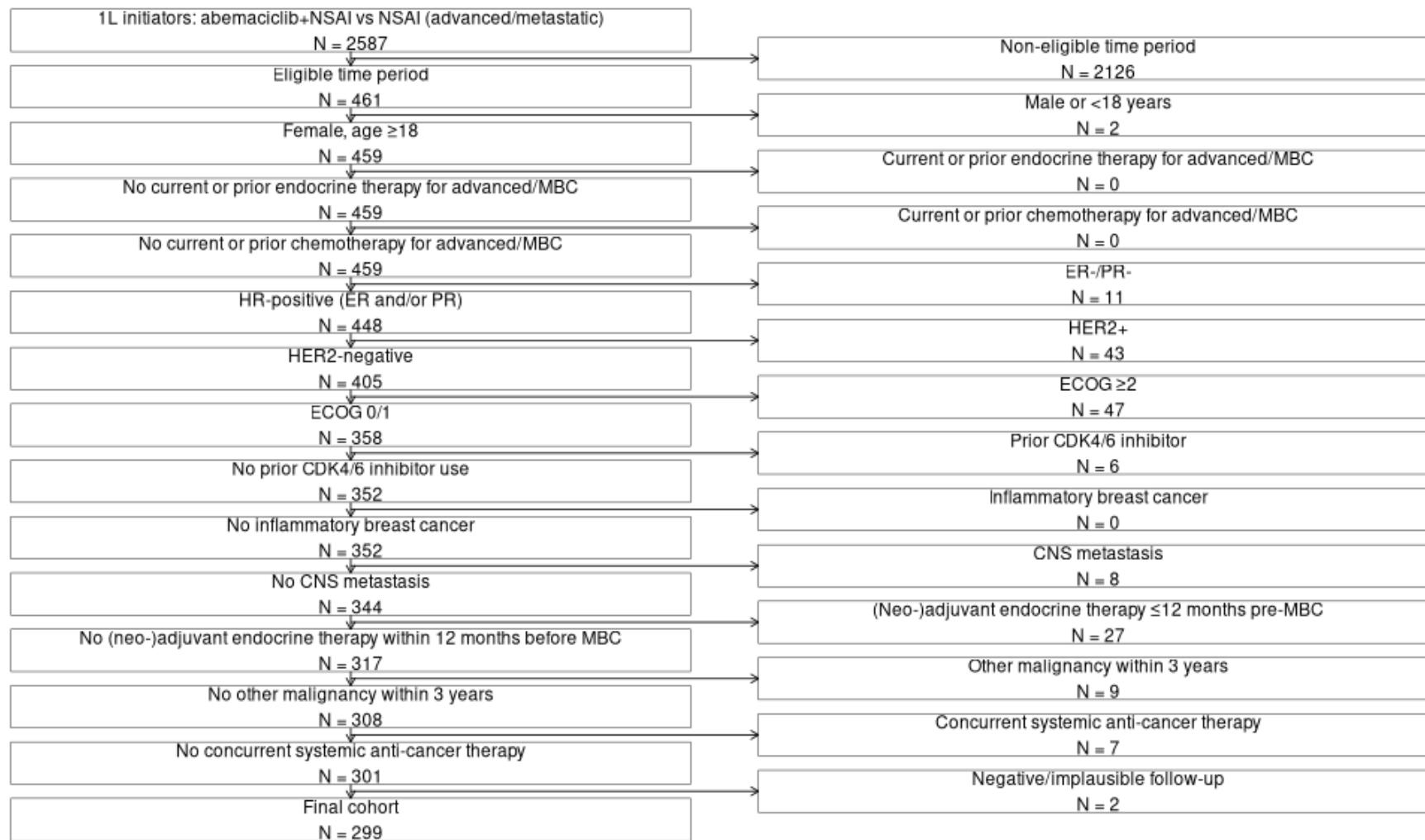
edb1 attrition



Abbreviations: NSAI = non-steroidal aromatase inhibitor (letrozole/anastrozole); MBC = metastatic breast cancer; HER2 = human epidermal growth factor receptor 2; CNS = central nervous system

Figure 5. CONSORT attrition to select eligible MONARCH-3-like populations in EDB3.

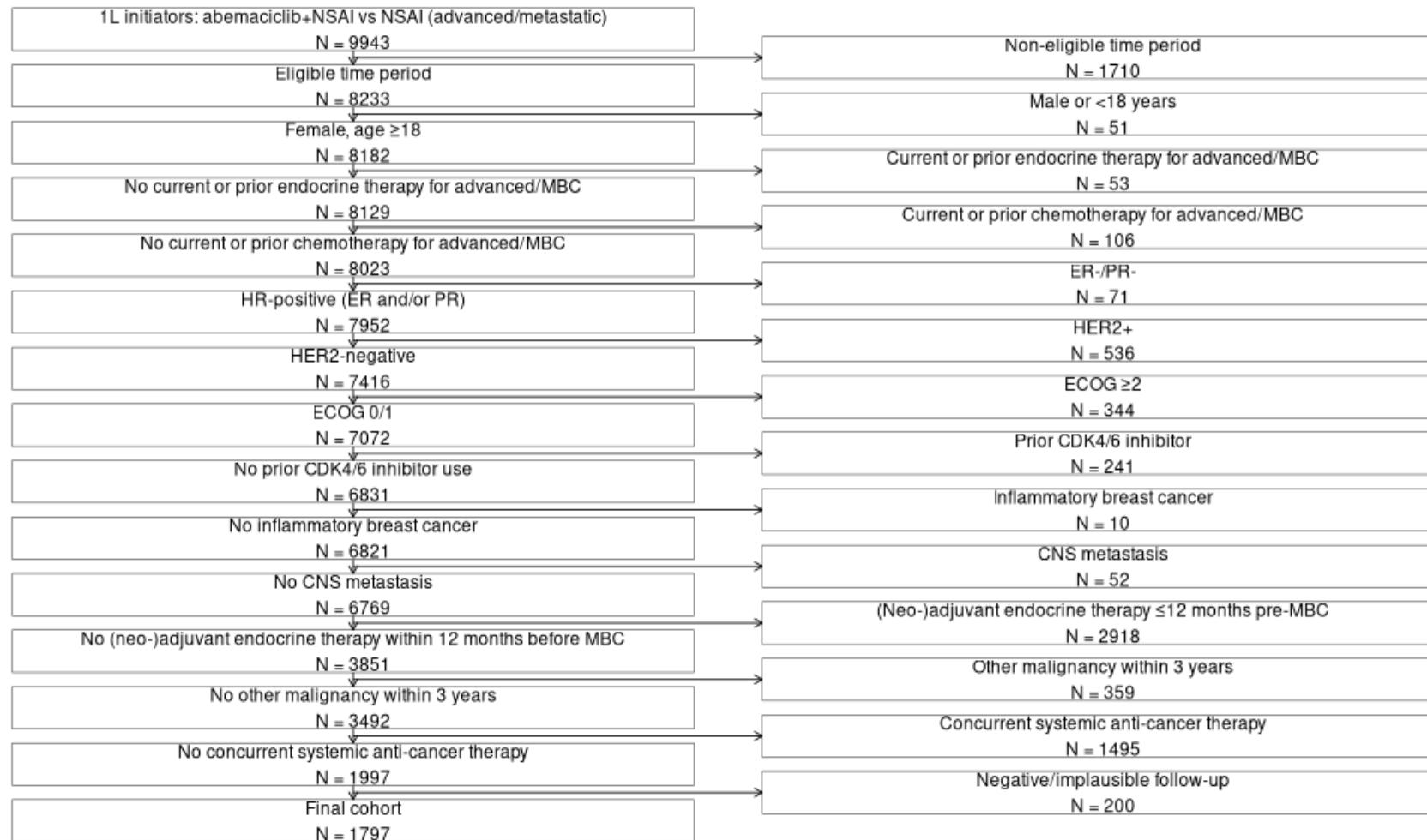
edb3 attrition



Abbreviations: NSAI = non-steroidal aromatase inhibitor (letrozole/anastrozole); MBC = metastatic breast cancer; HER2 = human epidermal growth factor receptor 2; CNS = central nervous system

Figure 6. CONSORT attrition to select eligible MONARCH-3-like populations in EDB4.

edb4 attrition



Abbreviations: NSAI = non-steroidal aromatase inhibitor (letrozole/anastrozole); MBC = metastatic breast cancer; HER2 = human epidermal growth factor receptor 2; CNS = central nervous system

10.2. Covariate balance figures

The following figures illustrate the balance of key covariates included in propensity score models among eligible MONARCH-3-like populations in EDB1, EDB3 and EDB4, respectively.

Figure 7. EDB1 covariate balance of covariates included in propensity score model before and after matching.

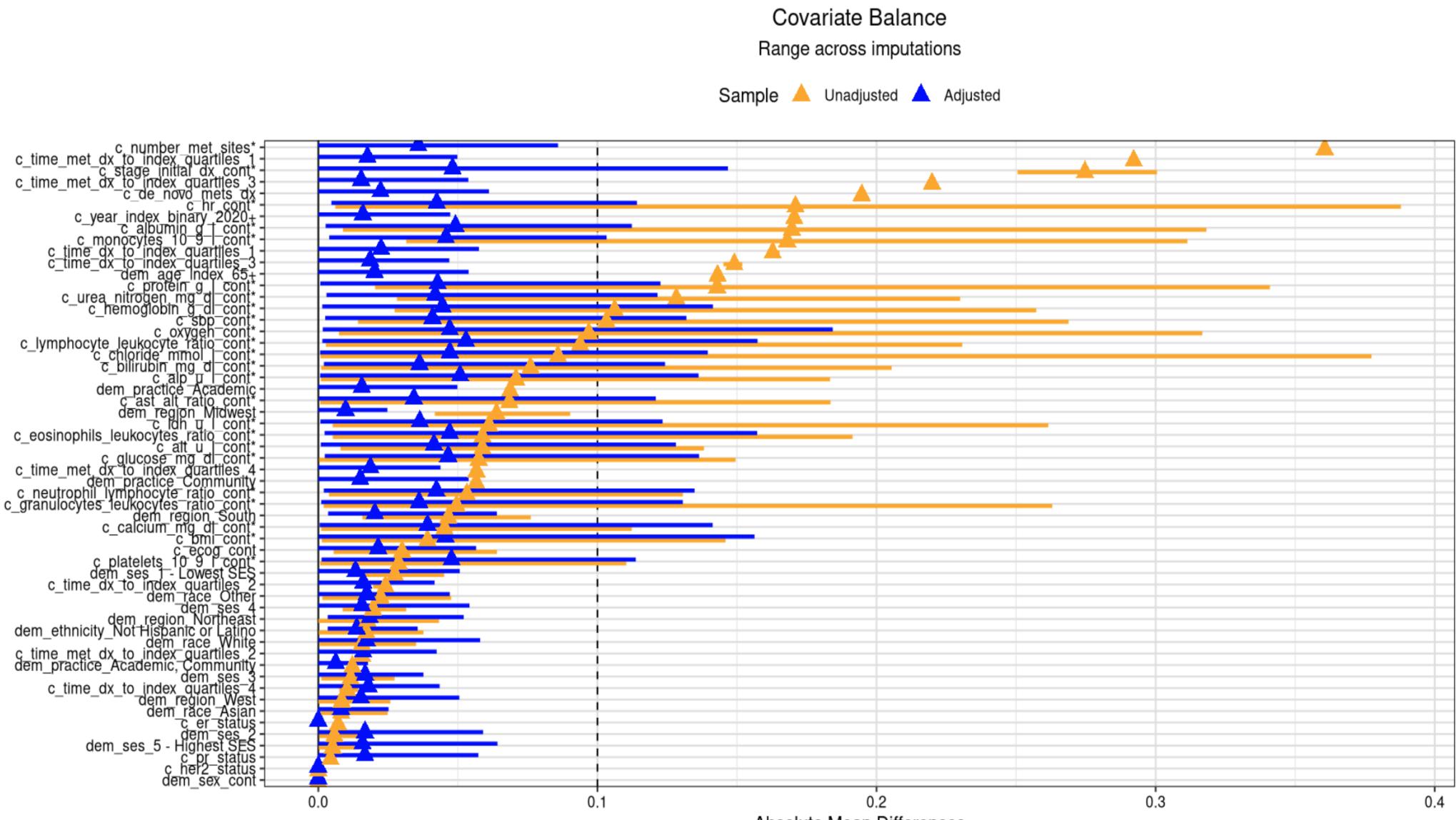
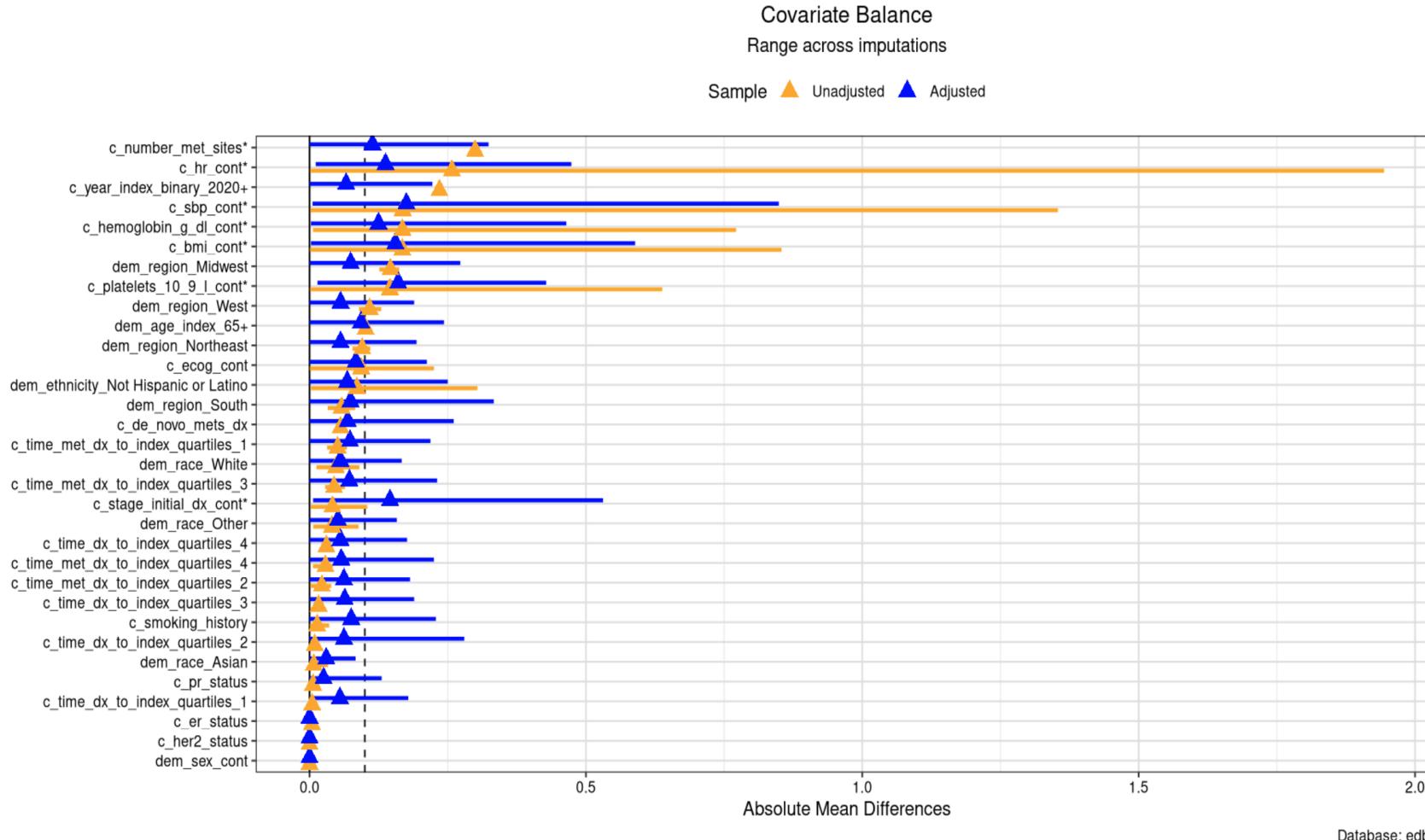


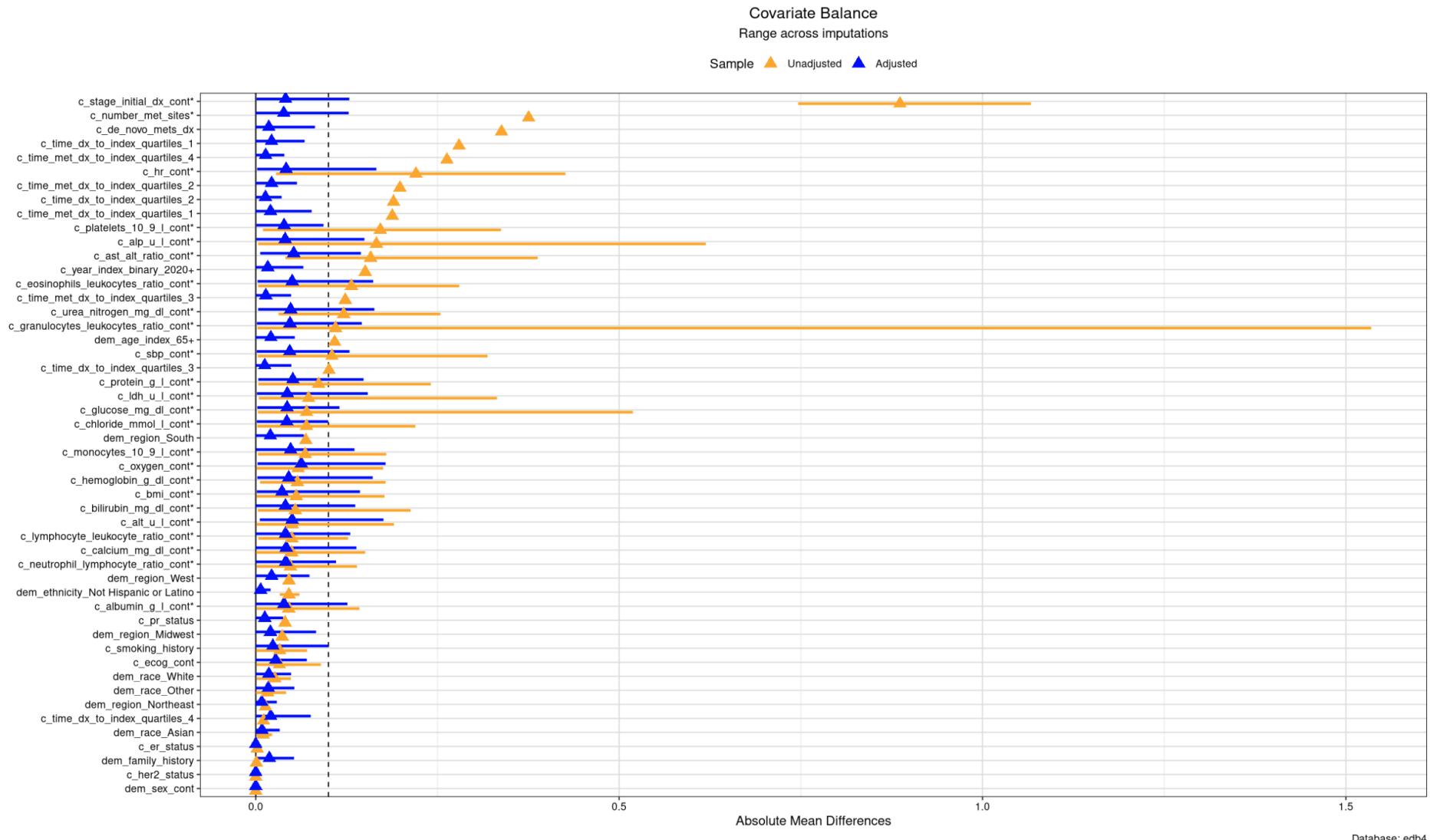
Figure 8. EDB3 covariate balance of covariates included in propensity score model before and after matching.



In EDB3, following variable was removed due to too many missings relative to number of covariates and study size after applying the inclusion/exclusion criteria:

c_albumin_g_l_cont, c_alp_u_l_cont, c_alt_u_l_cont, c_ast_alt_ratio_cont, c_bilirubin_mg_dl_cont, c_calcium_mg_dl_cont, c_chloride_mmol_l_cont, c_eosinophils_leukocytes_ratio_cont, c_glucose_mg_dl_cont, c_granulocytes_leukocytes_ratio_cont, c_ldh_u_l_cont, c_lymphocyte_leukocyte_ratio_cont, c_monocytes_10_9_l_cont, c_neutrophil_lymphocyte_ratio_cont, c_oxygen_cont, c_protein_g_l_cont, c_urea_nitrogen_mg_dl_cont.

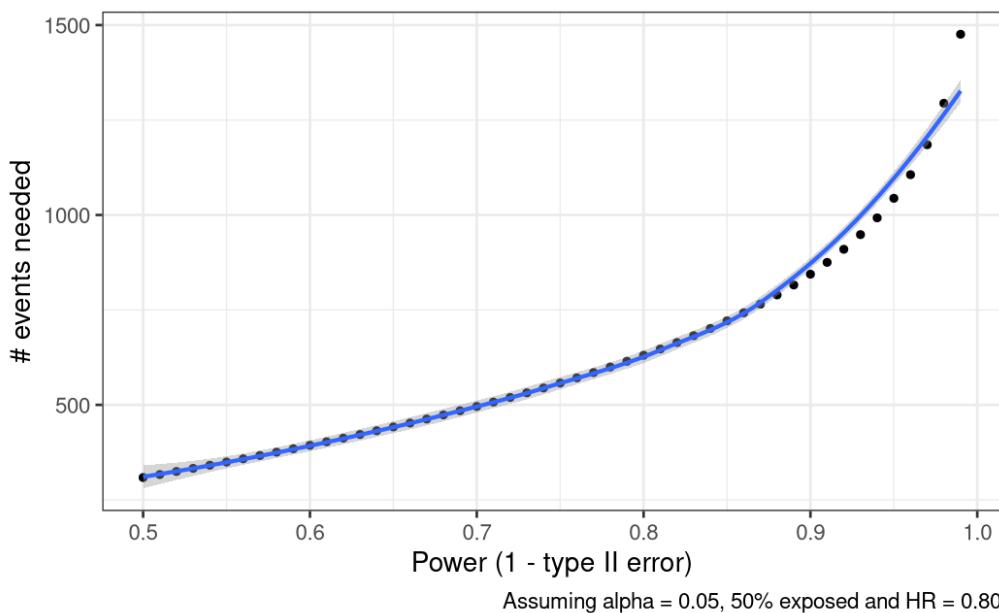
Figure 9. EDB4 covariate balance of covariates included in propensity score model before and after matching.



10.3. Sample size/power calculations

Power estimations are computed based on the average number of observed events across imputed and matched datasets according to the methodology described by Schoenfeld.³⁹ The OS result was null in the trial, therefore, we are not expecting to observe a strong effect in the emulation. Because one of our 1:1-matched samples, EDB1 (n = 570), used in the primary analysis, is larger than the trial sample (n = 493), we expect its confidence intervals to be narrower. In contrast, for EDB4 (n = 458) (primary analysis) and EDB3 (n = 72) (sensitivity analysis), which are smaller than the trial sample, we expect wider confidence intervals.

Figure 10 Number of events needed to achieve X power for overall-survival outcome



Primary analysis:

- Based on a total of 188 events in the 1:1-matched set in EDB1, we would achieve a power of 0.33 to detect an effect as large or larger than HR = 0.80.
- Based on a total of 135 events in the 1:1-matched set in EDB4, we would achieve a power of 0.25 to detect an effect as large or larger than HR = 0.80.

Sensitivity analysis:

- Based on a total of 28 events in the 1:1-matched set in EDB3, we would achieve a power of 0.09 to detect an effect as large or larger than HR = 0.80.

Thus, our study will be underpowered for the OS outcome, akin to the original trial that was not powered for OS.

10.4. Additional Figures and Tables

Table 9. Lab measurement plausibility thresholds.

Lab and standardized unit	Lower plausibility threshold	Upper plausibility threshold
c_albumin_g_l	10	200
c_alp_u_l	1	2000
c_alt_u_l	1	90000
c_ast_u_l	1	90000
c_bilirubin_mg_dl	0.1	80
c_calcium_mg_dl	0.1	20
c_chloride_mmol_l	0.1	200
c_eosinophils_leukocytes_ratio	0	100
c_glucose_mg_dl	0.1	2000
c_granulocytes_leukocytes_ratio	0	100
c_hemoglobin_g_dl	0.1	20
c_ldh_u_l	0.1	Inf
c_lymphocyte_10_9_l	0	1e+06
c_lymphocyte_leukocyte_ratio	0	100
c_monocytes_10_9_l	0	1e+06
c_neutrophil_10_9_l	0	1e+06
c_platelets_10_9_l	0	5000
c_protein_g_l	1	300
c_urea_nitrogen_mg_dl	0.1	250

Table 10. Vital sign measurement plausibility thresholds.

Vital sign	Lower plausibility threshold	Upper plausibility threshold
c_sbp	50	250
c_dbp	30	150
c_bmi	10	80
c_bsa	0.5	3.5
c_height	0.5	3
c_oxygen	50	100
c_pain	0	10
c_hr	20	250
c_resp	5	50
c_temp	86	113
c_weight	20	300

Table 11. Mapping from State to Region.

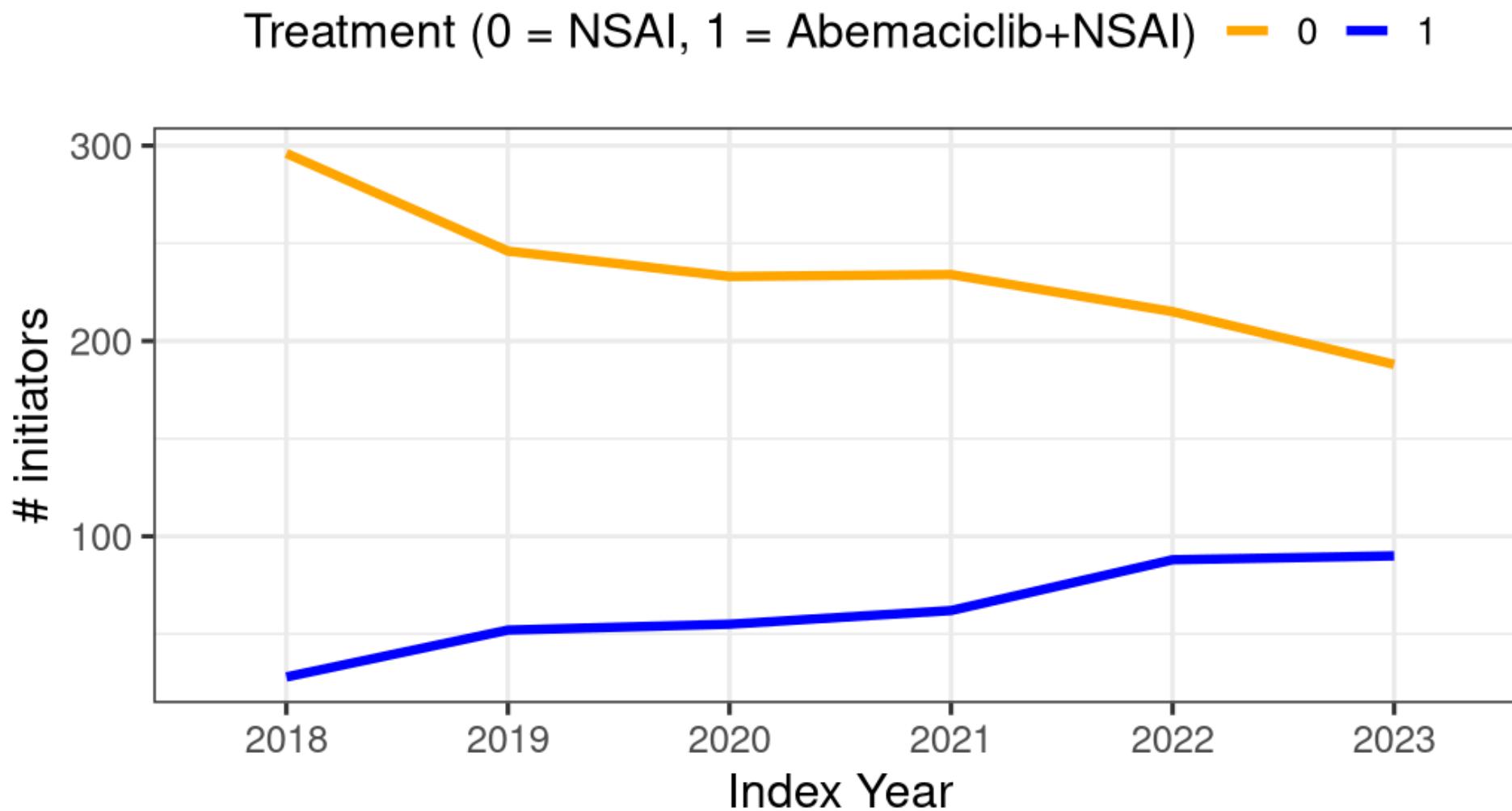
State	Region
CT	Northeast
ME	Northeast
MA	Northeast
NH	Northeast
RI	Northeast
VT	Northeast
DE	Northeast
NJ	Northeast
NY	Northeast
PA	Northeast
IL	Midwest
IN	Midwest
MI	Midwest
OH	Midwest
WI	Midwest
IA	Midwest
KS	Midwest
MN	Midwest
MO	Midwest
NE	Midwest
ND	Midwest

SD	Midwest
FL	South
GA	South
MD	South
NC	South
SC	South
VA	South
DC	South
WV	South
AL	South
KY	South
MS	South
TN	South
AR	South
LA	South
OK	South
TX	South
AZ	West
CO	West
ID	West
MT	West
NV	West
NM	West

UT	West
WY	West
AK	West
CA	West
HI	West
OR	West
WA	West

Figure 11. Treatment initiation trends by calendar year and treatment in EDB1.

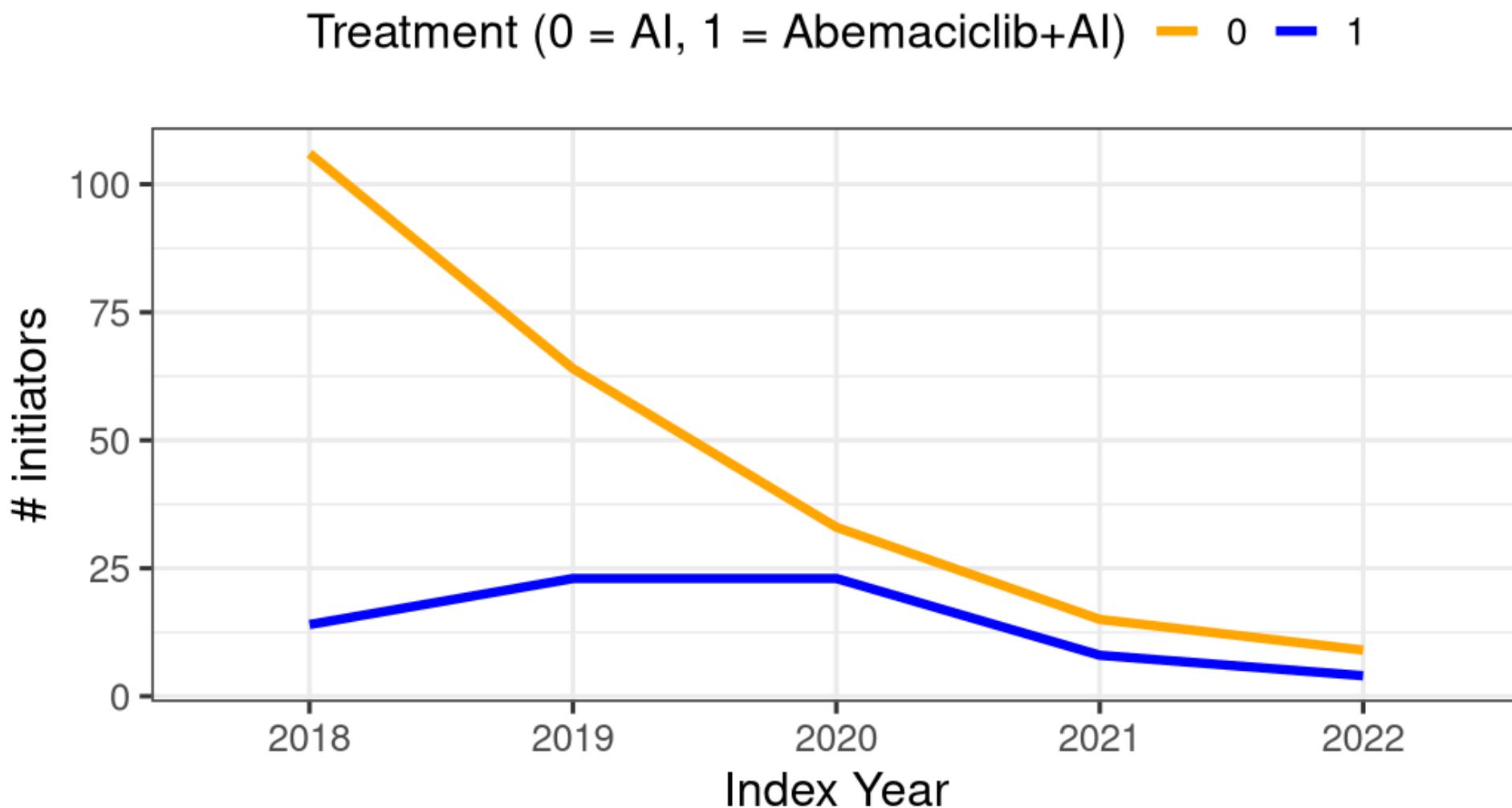
Treatment initiation trends in edb1



Abbreviations: NSAI = non-steroidal aromatase inhibitor (letrozole/anastrozole)

Figure 12. Treatment initiation trends by calendar year and treatment in EDB3.

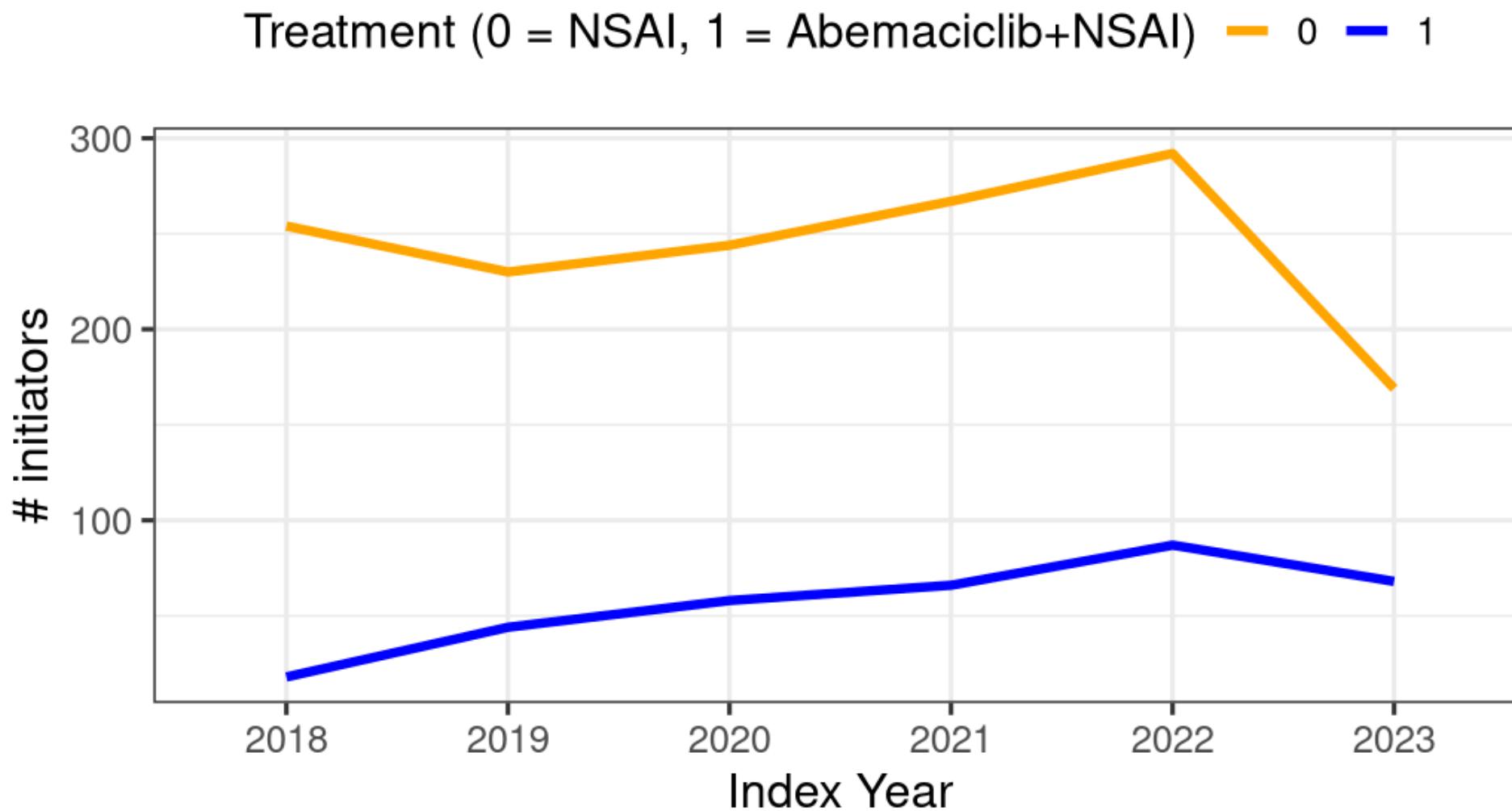
Treatment initiation trends in edb3



Abbreviations: NSAI = non-steroidal aromatase inhibitor (letrozole/anastrozole)

Figure 13. Treatment initiation trends by calendar year and treatment in EDB4.

Treatment initiation trends in edb4



Abbreviations: NSAI = non-steroidal aromatase inhibitor (letrozole/anastrozole)

NCTID	NCT02246621
Acronym	MONARCH3
Protocol	https://www.dropbox.com/scl/fi/nz84xecsr70oa048pqu5s/MONARCH3_Protocol.pdf?rlkey=vgo46zxbui47ba945sdev06vi&st=xmnbqwz&dl=0
PMID	28968163
Indication	Breast cancer
Line of Therapy	Metastatic (first-line)
Exposure	Abemaciclib plus nonsteroidal aromatase inhibitor - abemaciclib 150 mg orally twice daily, continuous schedule, in combination with either letrozole 2.5 mg orally once daily (continuous) or anastrozole 1 mg orally once daily (continuous).
Comparisons	Placebo plus nonsteroidal aromatase inhibitor - placebo orally twice daily, continuous schedule, in combination with either letrozole 2.5 mg orally once daily (continuous) or anastrozole 1 mg orally once daily (continuous).
Emulated outcome	Overall survival (secondary endpoint in original trial)

Key Inclusion/Exclusion Criteria						Comment
Criteria	RCT eligibility criteria (taken from the original trial protocol)	Relevance for emulation	Emulation [EDB1]	Emulation [EDB3]	Emulation [EDB4]	
Inclusion	<p>Have a diagnosis of HR+ HER2- breast cancer. Although not required as a protocol procedure, metastatic disease should be considered for biopsy whenever possible to reassess HR and HER2 status if clinically indicated.</p> <ul style="list-style-type: none"> • To fulfill the requirement for HR+ disease, a breast cancer must express, by immunohistochemistry (IHC), at least one of the hormone receptors (ER, progesterone receptor [PgR]) as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010). • To fulfill the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization (ISH) as defined in the relevant ASCO/CAP guidelines (Wolff et al. 2013). 	Relevant	Possible	Possible	Possible	<p>Keep if HR+ (ER+ or PR+) or missing because:</p> <ul style="list-style-type: none"> - Abemaciclib + letrozole is indicated for HR+/HER2-negative metastatic breast cancer. <p>Keep if HER2-negative or HER2 status unknown because:</p> <ul style="list-style-type: none"> - Ribociclib + letrozole is indicated for HR+/HER2-negative metastatic breast cancer. - Letrozole monotherapy was historically the standard first-line treatment for HR+/HER2-negative metastatic breast cancer before CDK4/6 inhibitors became standard of care - In HER2+ HR+ metastatic breast cancer, letrozole is not typically given alone; instead, it is usually combined with anti-HER2 therapy (e.g., trastuzumab ± pertuzumab).
Inclusion	Have locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease	Relevant	Possible	Possible	Possible	
Inclusion	<p>Have postmenopausal status, defined as meeting one of the following conditions:</p> <ul style="list-style-type: none"> • Prior bilateral oophorectomy • Age \geq60 years • Age $<$60 years and amenorrheic (non-treatment-induced amenorrhea secondary to tamoxifen, toremifene, ovarian suppression, or chemotherapy) for at least 12 months. Follicle-stimulating hormone (FSH) and estradiol must be in the postmenopausal range. 	Relevant	Limited	Limited	Limited	<p>To protect privacy, most databases only provide month- or year-level granularity of dates; post-menopausal status can be defined based on age and inferred by the fact that abemaciclib was administered (indication in postmenopausal women)</p>
Inclusion	<p>Have one of the following as defined by the RECIST v1.1:</p> <ul style="list-style-type: none"> • Measurable disease • Nonmeasurable bone-only disease. Nonmeasurable bone-only disease may include any of the following: blastic bone lesions, lytic bone lesions without a measurable soft tissue component, or mixed lytic/blastic bone lesions without a measurable soft tissue component. 	Relevant	Limited	Limited	Limited	<p>We are assuming that all subjects in RWD have measurable disease if they are receiving treatment</p>

Inclusion	Have a PS of ≤1 on the ECOG scale	Relevant	Possible	Possible	Possible	ECOG implementation possible; high % missingness likely
Inclusion	Have adequate organ function, including: <ul style="list-style-type: none">• hematologic: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, and hemoglobin $\geq 8 g/dL$. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after the erythrocyte transfusion.• hepatic: bilirubin ≤ 1.5 times the upper limit of normal (ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 times ULN (or ALT and AST ≤ 5 times ULN if liver metastases are present).• renal: serum creatinine ≤ 1.5 times ULN.	Relevant	Not implementable	Not implementable	Not implementable	Not captured well
Inclusion	Have discontinued previous localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture at least 2 weeks prior to randomization and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy	Limited relevance	Not implementable	Not implementable	Not implementable	Not captured well
Inclusion	Are female and ≥18 years of age	Relevant	Possible	Possible	Possible	
Inclusion	Are able to swallow capsules	Limited relevance	Not implementable	Not implementable	Not implementable	
Inclusion	Have given written informed consent prior to any study-specific procedures	Limited relevance	Not implementable	Not implementable	Not implementable	
Inclusion	Are reliable, willing to be available for the duration of the study, and are willing to follow study procedures.	Limited relevance	Not implementable	Not implementable	Not implementable	
Inclusion	Restriction to period 2017-2023	Relevant	Possible	Possible	Possible	2017 was the approval year for abemaciclib, and 2023 is the end of the available data stream
Exclusion	Have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.	Relevant	Not implementable	Not implementable	Not implementable	Since treatment was given, it is reasonable to assume that patients did not have severe organ dysfunction
Exclusion	Have inflammatory breast cancer.	Relevant	Possible	Possible	Possible	Record of inflammatory breast cancer
Exclusion	Have clinical evidence or a history of CNS metastasis. Screening is not required for enrollment	Relevant	Possible	Possible	Possible	Record of CNS metastases
Exclusion	Are currently receiving or have previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer. [Note: A patient may be enrolled if she received prior (neo)adjuvant endocrine therapy (including, but not limited to anti-estrogens or aromatase inhibitors) for localized disease. In addition, a patient may be enrolled if she has received ≤2 weeks of NSAI in this disease setting immediately preceding screening and agrees to discontinue NSAI until study treatment initiation.]	Relevant	Possible	Possible	Possible	Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole
Exclusion	Have received prior (neo)adjuvant endocrine therapy (e.g., anti-estrogens or aromatase inhibitors) with a disease-free interval ≤12 months from completion of treatment.	Relevant	Possible	Possible	Possible	
Exclusion	Are currently receiving or have previously received chemotherapy for locoregionally recurrent or metastatic breast cancer. [Note: Patients may be enrolled if they received prior (neo)adjuvant chemotherapy for localized disease.]	Relevant	Possible	Possible	Possible	Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole
Exclusion	Have received prior treatment with everolimus	Relevant	Not implementable	Not implementable	Not implementable	Not well captured
Exclusion	Have received prior treatment with any CDK4/6 inhibitor (or participated in any CDK4/6 inhibitor clinical trial for which treatment assignment is still blinded)	Relevant	Possible	Possible	Possible	
Exclusion	Have initiated bisphosphonates or approved RANK ligand (RANK-L) targeted agents (for example, denosumab) <7 days prior to randomization	Relevant	Not implementable	Not implementable	Not implementable	Not captured well

Exclusion	Are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the investigator and Lilly clinical research physician (CRP) is required to establish eligibility	Limited relevance	Not implementable	Not implementable	Not implementable	Not captured well
Exclusion	Have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of randomization for a nonmyelosuppressive or myelosuppressive agent, respectively.	Limited relevance	Not implementable	Not implementable	Not implementable	Not captured well
Exclusion	Have had major surgery within 14 days prior to randomization to allow for post-operative healing of the surgical wound and site(s)	Relevant	Not implementable	Not implementable	Not implementable	Since treatment was given, it is reasonable to assume that patients did not undergo recent major surgery
Exclusion	Have received recent (within 28 days prior to randomization) yellow fever vaccination	Limited relevance	Not implementable	Not implementable	Not implementable	Not captured well
Exclusion	Have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis).	Relevant	Not implementable	Not implementable	Not implementable	Not captured well
Exclusion	Have a personal history within the last 12 months of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest	Relevant	Not implementable	Not implementable	Not implementable	Not captured well
Exclusion	Have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years.	Relevant	Limited	Limited	Not implementable	EDB4 does not contain records on diagnoses of other malignancies besides breast cancer
Exclusion	Have received an autologous or allogeneic stem-cell transplant	Limited relevance	Not implementable	Not implementable	Not implementable	Not available
Exclusion	Have active bacterial or fungal infection or detectable viral infection (for example, human immunodeficiency virus [HIV] or viral hepatitis). Screening is not required for enrollment	Limited relevance	Not implementable	Not implementable	Not implementable	Since treatment was given, it is reasonable to assume that patients did not have active bacterial or fungal infection or detectable viral infection

NCTID	NCT02246621
Acronym	MONARCH3
Protocol	https://www.dropbox.com/scl/fi/nz84xecsr70oa048pqu5s/MONARCH3_Protocol.pdf?rlkey=vgo46zxbui47ba945sdev06vi&st=xmvbqwz&dl=0
PMID	28968163
Indication	Breast cancer
Line of Therapy	Metastatic (first-line)
Exposure	Abemaciclib plus nonsteroidal aromatase inhibitor - abemaciclib 150 mg orally twice daily, continuous schedule, in combination with either letrozole 2.5 mg orally once daily (continuous) or anastrozole 1 mg orally once daily (continuous).
Comparisons	Placebo plus nonsteroidal aromatase inhibitor - placebo orally twice daily, continuous schedule, in combination with either letrozole 2.5 mg orally once daily (continuous) or anastrozole 1 mg orally once daily (continuous).
Emulated outcome	Overall survival (secondary endpoint in original trial)

Measurement eligibility criteria						Comment	encore.io function
Criteria	Criteria rule as defined in original protocol	Time point/period of emulated measurement [days]	Emulation [EDB1]	Emulation [EDB3]	Emulation [EDB4]		
Inclusion 1	<p>Have a diagnosis of HR+, HER2- breast cancer. Although not required as a protocol procedure, metastatic disease should be considered for biopsy whenever possible to reassess HR and HER2 status if clinically indicated.</p> <ul style="list-style-type: none"> • To fulfill the requirement for HR+ disease, a breast cancer must express, by immunohistochemistry (IHC), at least one of the hormone receptors (ER, progesterone receptor [PgR]) as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010). • To fulfill the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization (ISH) as defined in the relevant ASCO/CAP guidelines (Wolff et al. 2013). 	[-inf; 0]	<ul style="list-style-type: none"> - Any hormone-positive or hormone-missing status to or on index date - Any HER2-negative or HER2-missing status prior to or on index date 	<ul style="list-style-type: none"> - Any hormone-positive or hormone-missing status to or on index date - Any HER2-negative or HER2-missing status prior to or on index date 	<ul style="list-style-type: none"> - Any hormone-positive or hormone-missing status to or on index date - Any HER2-negative or HER2-missing status prior to or on index date 	<p>- If estrogen receptor or progesterone receptor missing and a patient received the exposures of interest, then is likely to be positive given the alignment with the indication for the exposures of interest</p> <p>- If HER2 is missing and a patient received the exposures of interest, then HER2 is likely to be negative given the alignment with the indication for the exposures of interest</p>	<p>edb_get_biomarker() edb_get_her2()</p>
Inclusion 2	Have locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease	[-inf; 0]	<p>First line of therapy needs to be for "Advanced" setting (LoT table);</p> <p>No systemic anti-cancer therapy following initial record potentially indicating metastatic disease and prior to index date</p>	<p>First line of therapy needs to be for "Advanced" setting (LoT table);</p> <p>No systemic anti-cancer therapy following initial record potentially indicating metastatic disease and prior to index date</p>	<p>Any evidence of at least one distant metastasis at any time before the index date (inclusive). This captures both de novo metastatic patients and those who progressed/developed metastases before/on the index date.</p> <p>First therapy for advanced disease after date of first metastasis.</p>	<p>EDB4 does not have a well-curated line of therapy variable</p>	<p>EDB4: Derived from edb_get_diagnosis_solid()</p>
Inclusion 3	Have postmenopausal status, defined as meeting one of the following conditions:	NA	NA	NA	NA	Although not directly captured in RWD, it is likely to be fulfilled given the alignment with the indication for the exposures of interest	

Inclusion 4	Have one of the following as defined by the RECIST v1.1: <ul style="list-style-type: none">• Measurable disease• Nonmeasurable bone-only disease. Nonmeasurable bone-only disease may include any of the following: blastic bone lesions, lytic bone lesions without a measurable soft tissue component, or mixed lytic/blastic bone lesions without a measurable soft tissue component.	NA	NA	NA	NA	It is reasonable to assume that all patients in RWD had measurable disease if they received treatment	
Inclusion 5	Have a Performance status of ≤ 1 on the ECOG scale	[-90; 0]	ECOG = 0 1	ECOG = 0 1	ECOG = 0 1		edbx_get_ecog()
Inclusion 6	Are female and ≥ 18 years of age	[0; 0]	Female and age ≥ 18 years	Female and age ≥ 18 years	Female and age ≥ 18 years		edbx_get_demographic()
Inclusion 7	Restriction to period 2017-2023	[0; 0]	Years 2017-2023	Years 2017-2023	Years 2017-2023		
Exclusion 1	Have inflammatory breast cancer.	[-inf; 0]	Record of inflammatory breast cancer	Record of inflammatory breast cancer	Record of inflammatory breast cancer		
Exclusion 2	Have clinical evidence or a history of CNS metastasis. Screening is not required for enrollment	[-inf; 0]	Record of CNS metastases prior to or on index date	Record of CNS metastases prior to or on index date	Record of CNS metastases prior to or on index date		edbx_get_diagnosis_solid()
Exclusion 3	Are currently receiving or have previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer. [Note: A patient may be enrolled if she received prior (neo)adjuvant endocrine therapy (including, but not limited to anti-estrogens or aromatase inhibitors) for localized disease. In addition, a patient may be enrolled if she has received ≤ 2 weeks of NSAI in this disease setting immediately preceding screening and agrees to discontinue NSAI until study treatment initiation.]	NA	NA	NA	NA	Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole/anastrozole	
Exclusion 4	Have received prior (neo)adjuvant endocrine therapy (e.g., anti-estrogens or aromatase inhibitors) with a disease-free interval ≤ 12 months from completion of treatment.	[MBC-365; MBC-1] <i>MBC = first metastatic breast cancer date</i>	Treatment with (neo)adjuvant endocrine therapy ≤ 12 months from MBC <i>MBC = first metastatic breast cancer date</i>	No systemic anti-cancer therapy following initial record potentially indicating metastatic disease and prior to index date	No systemic anti-cancer therapy following initial record potentially indicating metastatic disease and prior to index date		
Exclusion 5	Are currently receiving or have previously received chemotherapy for locoregionally recurrent or metastatic breast cancer. [Note: Patients may be enrolled if they received prior (neo)adjuvant chemotherapy for localized disease.]	NA	NA	NA	NA	Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole/anastrozole	
Exclusion 6	Have received prior treatment with any CDK4/6 inhibitor (or participated in any CDK4/6 inhibitor clinical trial for which treatment assignment is still blinded)	[-inf; -1]	Prior treatment with CDK4/6	Prior treatment with CDK4/6	Prior treatment with CDK4/6		
Exclusion 7	Have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years.	[-1095; 0]	Record of cancer diagnosis within 1095 days prior to or on index day	Record of cancer diagnosis within 1095 days prior to or on index day	Record of non-index cancer treatment within 1095 days prior to or on index day	No diagnosis table for ED84 available	